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I Semester 1975-76

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MECHANISM FOR THE α -HALOGENATION OF SULFOXIDES

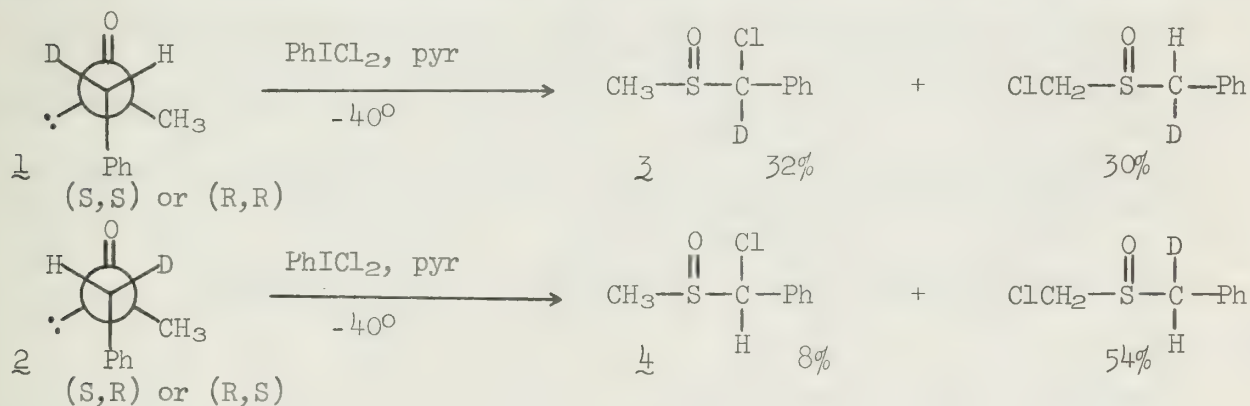
Reported by Charles Donley

August 25, 1975

Prior to 1968 the direct α -halogenation of sulfoxides had not been reported. A variety of halogenating agents have since been observed to convert dialkyl and aryl alkyl sulfoxides with at least one α -hydrogen to α -halo sulfoxides. Considerable interest has been generated concerning the mechanism of this reaction since several unusual effects have had to be accounted for. This seminar will trace the background and development of the mechanistic investigations for the α -halogenation of sulfoxides.

Chlorinating agents which have been used to effect the direct α -chlorination of sulfoxides are *p*-toluenesulfonyl chloride,¹ nitrosyl chloride,³ iodobenzene dichloride,^{4,6} *t*-butyl hypochlorite,⁸ chlorine,⁹ sulfuryl chloride,^{11,12} *N*-chlorobenzotriazole,¹⁴ and *N*-chlorosuccinimide.^{15,24} α -Bromination can be achieved by using *t*-butyl hypobromite,⁸ bromine,^{6c,10} *N*-bromosuccinimide/bromine,¹⁰ or *N*-bromosuccinimide/*p*-toluenesulfonic acid.²⁴ The only reported attempt at α -iodination with *N*-iodosuccinimide failed.²⁴ Since α -halo sulfoxides are sensitive to Pummerer type cleavage reactions of the S—O bond from the halo acids generated during the reaction,² the halogenations are usually performed in pyridine or in the presence of an insoluble, inorganic base (e.g. potassium acetate, potassium carbonate, or calcium oxide). Dihalogenation can also be achieved, but the monohalogenated sulfoxides are much less reactive toward further halogenation, thereby allowing for easy isolation of either the mono or dihalo sulfoxide.

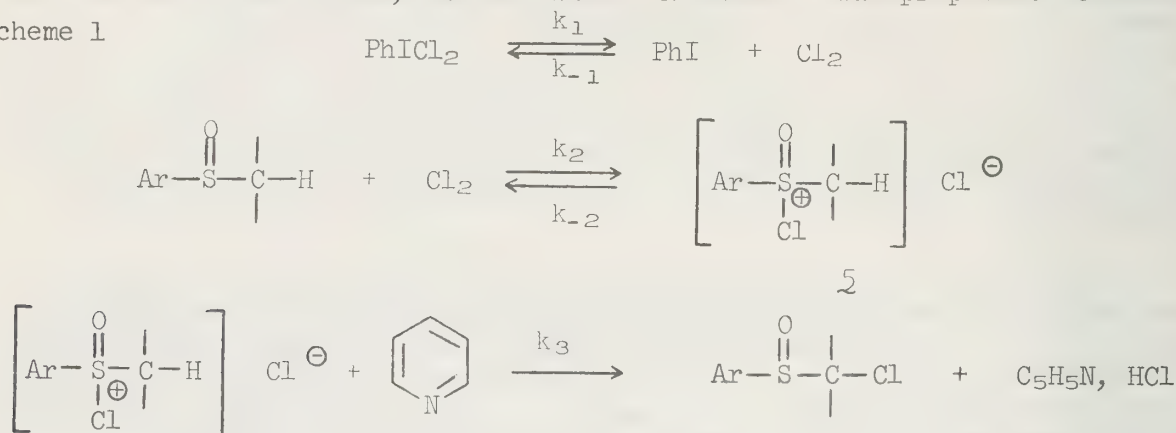
In general, α -halogenations carried out in the presence of pyridine are highly stereoselective but not very regioselective. In the absence of pyridine or in the presence of an insoluble, inorganic base, α -halogenation is highly regioselective but not stereoselective. Thus, Montanari *et al.*⁴ established early that when the α -carbon is a prochiral center, chlorination in the presence of pyridine involves the stereospecific formation of only one of the two possible diastereomeric α -chlorosulfoxides. Chlorination of α -deuteriobenzyl methyl sulfoxide **1** and the diastereomer **2** with iodobenzene dichloride gave α -chloro- α -deuteriobenzyl methyl sulfoxide **3** and α -chlorobenzyl methyl sulfoxide **4**, respectively, as well as the chloromethyl sulfoxides. No α -chlorobenzyl methyl sulfoxide **4** could be detected in the first



reaction and no α -chloro- α -deuteriobenzyl methyl sulfoxide **3** was found in the second. Sulfoxide **1** was obtained from stereoselective H-D exchange from benzyl methyl sulfoxide and **2** from α,α -dideuteriobenzyl methyl sulfoxide. Evidently, α -halogenations in pyridine involve the stereospecific replacement of the proton

In 1971 a detailed kinetic investigation¹⁸ was carried out on the α -chlorination of sulfoxides by iodobenzene dichloride/pyridine in acetonitrile at 0°. When *o*-chlorophenyl methyl sulfoxide was treated with PhICl_2 in an excess of pyridine and iodobenzene in acetonitrile, the experimentally determined rate was found to be directly proportional to the concentrations of sulfoxide, iodobenzene dichloride, and pyridine and indirectly proportional to the concentration of iodobenzene. A comparison of the rate constants for this sulfoxide and *o*-chlorophenyl trideuteriomethyl sulfoxide, revealed a kinetic isotope effect, $k_{\text{H}}/k_{\text{D}} = 5.5$. Also the effect of substituents was studied by comparing the rate constants for the above sulfoxide and 2-chloro-4-methylphenyl methyl sulfoxide, 2,4-dichlorophenyl methyl sulfoxide, and 2-chloro-4-acylphenyl methyl sulfoxide. A Hammett plot using Hammett's σ values gave a ρ value of -2.55 with a correlation coefficient of 0.9977. Based on the kinetic data, the mechanism in Scheme 1 was proposed. Utilizing

Scheme 1 k_1



the steady-state treatment, the rate of formation of α -chlorosulfoxide was given by equation (1). Since the intermediate 5 was not observed to accumu-

$$(1) \quad \frac{d[\alpha\text{-Chlorosulfoxide}]}{dt} = k_3 [\text{5}] [\text{pyr}] = \frac{k_2 k_3 [\text{Sulfoxide}] [\text{Cl}_2] [\text{pyr}]}{k_3 [\text{pyr}] + k_{-2}}$$

late, it was concluded that $k_{-2} \gg k_3$ [pyr]. The concentration of chlorine was expressed as $[Cl_2] = \frac{k_1 [PhICl_2]}{k_{-1} [PhI]}$ and substitution of this expression and

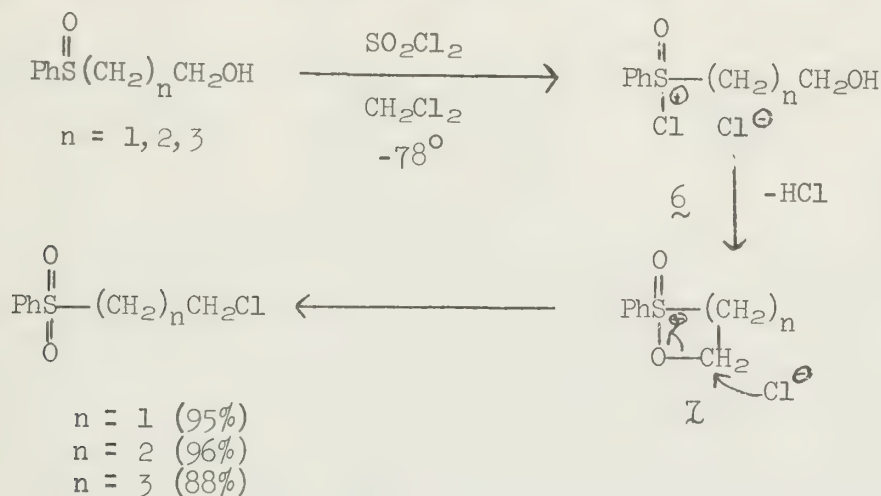
elimination of the k_3 [pyr] term lead to equation (2), identical to the experimentally determined rate law.

$$(2) \frac{d[\alpha\text{-Chlorosulfoxide}]}{dt} = \frac{k_1 k_2 k_3 [\text{Sulfoxide}] [\text{PhICl}_2] [\text{pyr}]}{k_{-1} k_{-2} [\text{PhI}]}$$

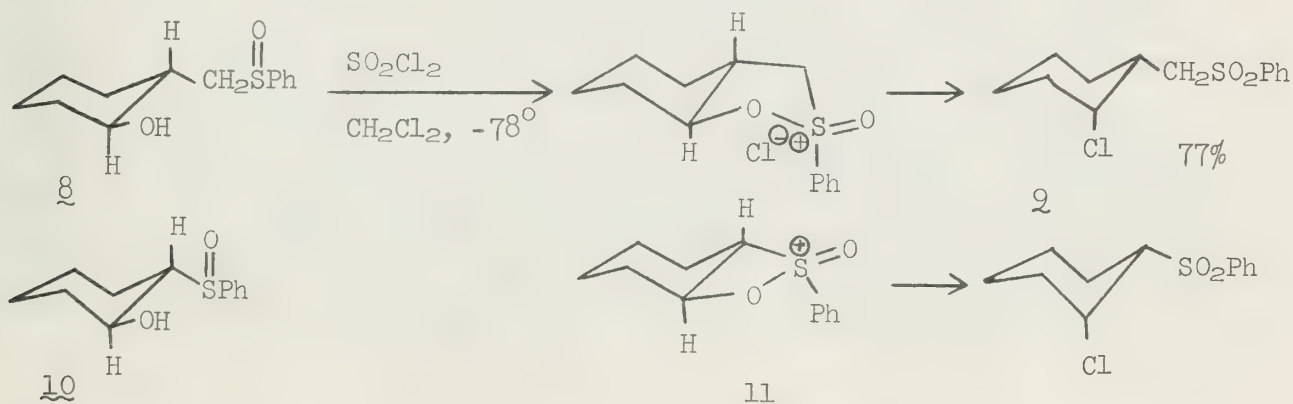
The last step in Scheme 1 was said to be rate-determining for substrates which were sterically hindered or deactivated by electron-withdrawing groups, in agreement with the large, experimentally determined isotope effect of 5.5. It was concluded that hydrogen abstraction from 5 must be followed by rapid chlorine migration to the α -carbon in a concerted process since no H-D exchange was observed by working in an excess of D_2O-H_2O . The large kinetic isotope effect and the absence of isotopic exchange thus ruled out an intermediate carbanion as exists in the halogenation of ketones. The large

ρ value of -2.55 indicated that the reaction was favored by electron-donating substituents in the aryl ring. Although electrophilic attack by chlorine is consistent with this large ρ value, the base abstraction of a proton should be favored by electron-withdrawing substituents. A small positive ρ value would be expected for proton abstraction since the electronic effects would be transmitted through the sulfur atom. The α -chlorination of benzylic sulfides by N-chlorosuccinimide does in fact give a ρ value of +1.1.¹⁷ The ρ value of -2.55, therefore, was interpreted as evidence for a transition state which resembles the intermediate 5, a chlorosulfoxonium ion. The magnitude of ρ , moreover, suggested that attack had occurred at sulfur rather than at oxygen. In comparison, protonation of sulfoxides, which involves attack at oxygen, has been shown to give a much smaller ρ (-0.72).¹⁸

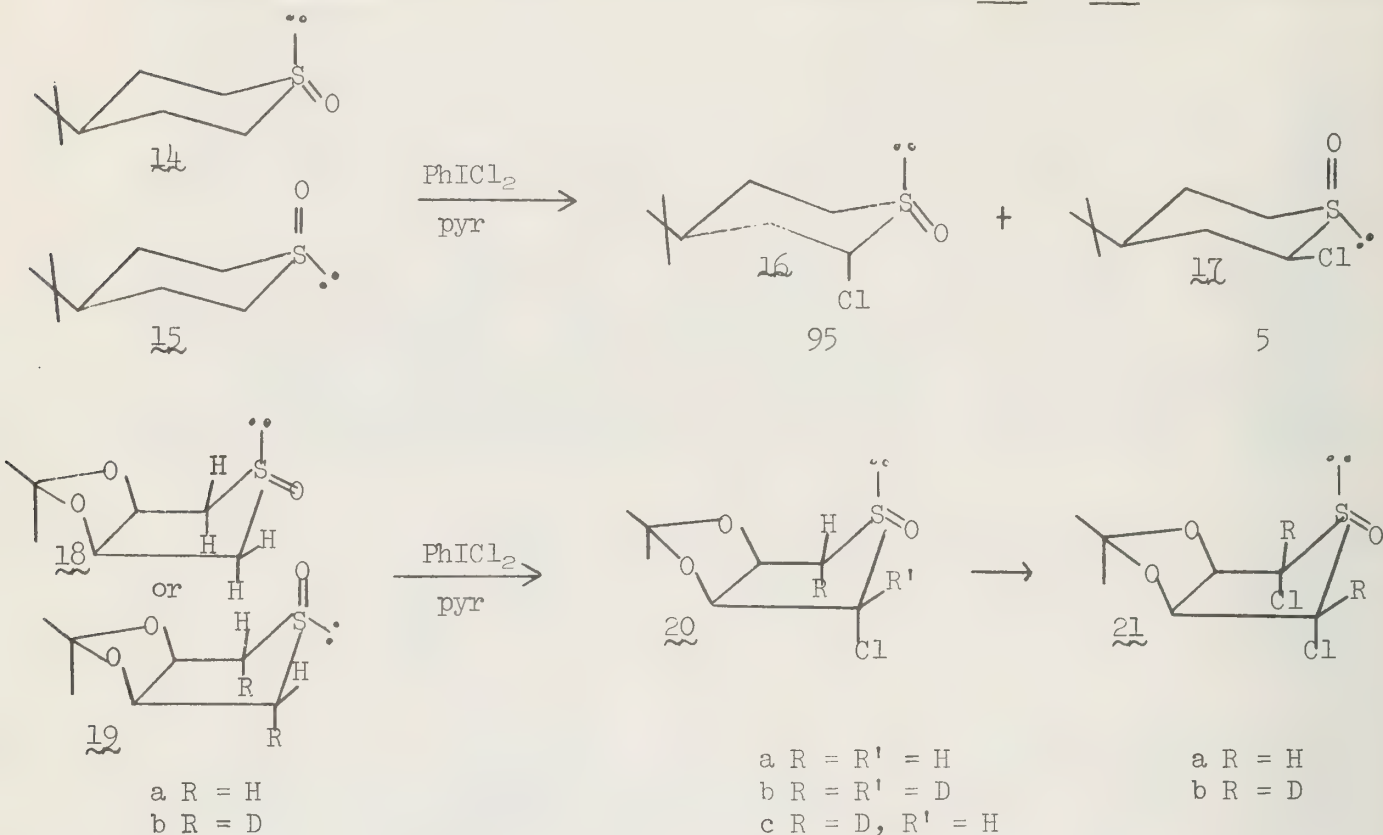
Additional evidence for the intermediacy of a chlorosulfoxonium ion was provided by Durst and Tin.^{13, 23} Sulfuryl chloride in the absence of pyridine was used to chlorinate sulfoxides containing an hydroxy group β , γ , or δ to sulfur. The results are summarized in Scheme 2. No α -chlorination was observed, but instead the corresponding β , γ , and δ -chloro sulfones were obtained in high yields. The formation of these products was rationalized as Scheme 2



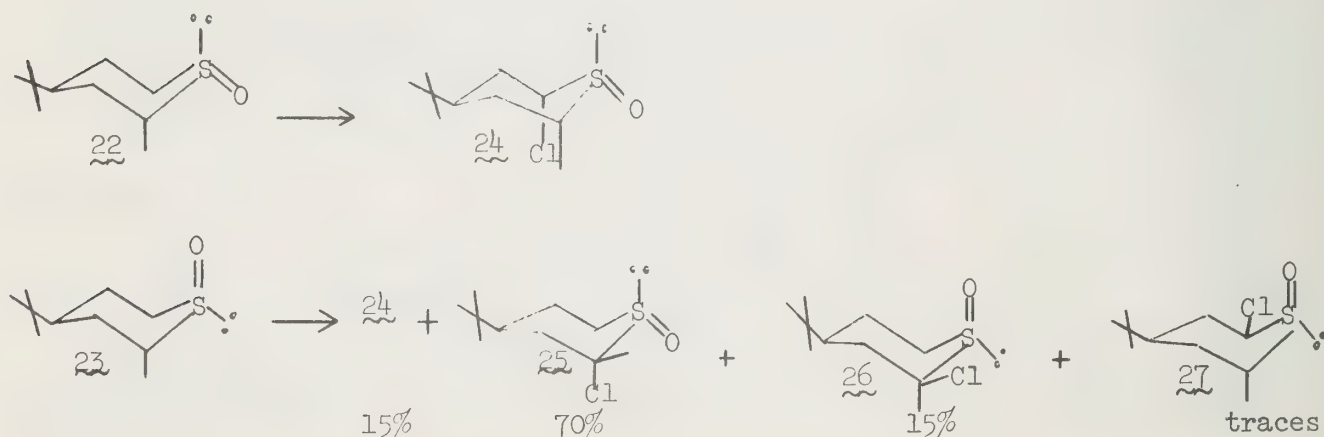
arising from intramolecular hydroxyl displacement of chloride from an initially formed chlorosulfoxonium ion 6 to yield a cyclic alkoxyoxosulfonium ion 7, which underwent subsequent ring opening via chloride counterion. When $n > 4$ no sulfones were obtained; instead α -chlorination occurred in high yields. This fact provides evidence for the existence of 7, since only when the OH function is in the β , γ , or δ position can favorable 4, 5, or 6-membered cyclic alkoxyoxosulfonium ions be formed. In addition, 8 was converted in 77% yield to 9, whereas 10 under the same conditions was not converted to a chloro sulfone. Conversion of 10 would have required a highly strained trans-6,4-cyclic alkoxyoxosulfonium ion intermediate 11.



Various studies^{20,21,22,27-29} on the α -halogenation of cyclic sulfoxides have been conducted. In particular the work of Marquet *et al.*²² was highly definitive. When either of the 4-*t*-butylthiane 1-oxides 14 or 15 was chlorinated with PhICl_2 in pyridine,⁴ the same α -chloro products 16 and 17 were obtained in a ratio of 95:5. Likewise, when 18a or 19a was chlorinated,

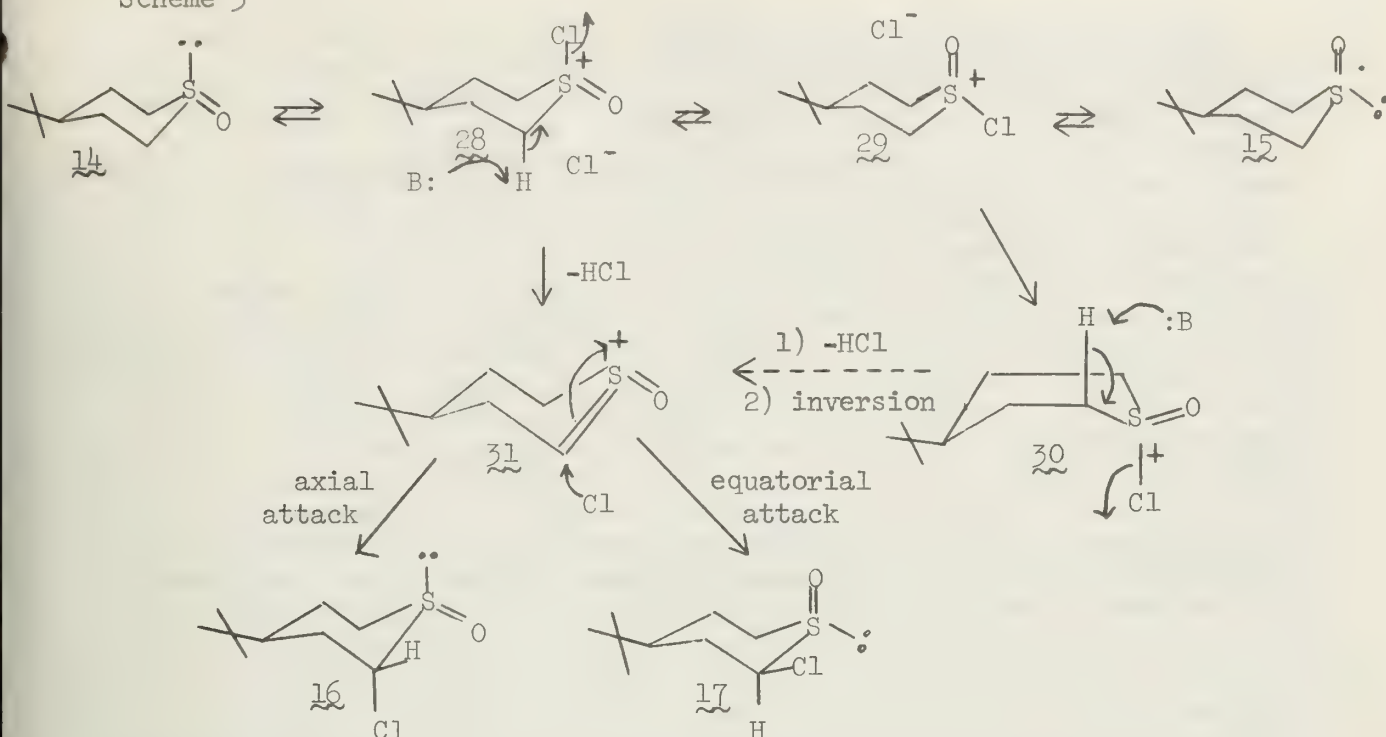


a single product 20a or 21a was obtained depending on whether one or two equivalents of PhICl_2 was used. The chlorination of monodeuterated 18b gave 20a and the chlorination of dideuterated 19b gave a mixture of 20b and 20c. Upon dichlorination 18b gave only 21a, whereas 19b gave a mixture of 21a and 21b. When the unsymmetrical monomethyl sulfoxide 22 was chlorinated, a single α -chloro sulfoxide product 24 was observed. However, when the isomer 23 was chlorinated, a mixture of products 24, 25, 26, and 27 were obtained.



To explain these unusual results, the mechanism in Scheme 3 was proposed. The first step in this mechanism was electrophilic attack by chlorine on the

Scheme 3

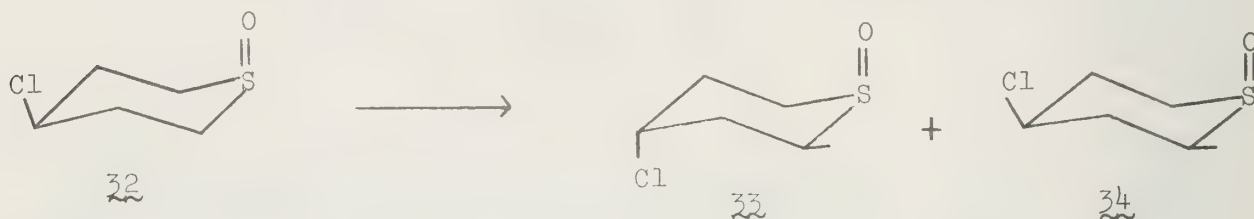


sulfinyl lone pair of electrons to form the chlorosulfoxonium ion intermediates, 28 or 29. The next step was conceived as base abstraction of an α -hydrogen to give a trans-diaxial elimination of HCl, a process which can only directly take place through the chlorosulfoxonium ion 28. The conformation of 29 was not suitably disposed for trans-diaxial elimination. It was proposed, however, that 29 could undergo elimination of HCl by two routes, depending on the nature of the substrate. The chlorosulfoxonium ion 29 could equilibrate with 28 by inversion of the sulfinyl group to the equatorial position through nucleophilic $\text{S}_{\text{N}}2$ displacement of chloride ion by the chloride counterion, or 29 could assume the boat conformation 30. In either case, the required trans-diaxial elimination of HCl could then be achieved to give the same intermediate 31 as obtained from 28. (Durst has called this new intermediate an "oxosulfenium ion"²⁴ and Klein and Stollar have described it as an "inverted ylide".²⁷) The last step in this mechanism was attack by chloride ion at the α -carbon in 31 to give the α -chlorosulfoxide product, axial attack being the preferred route.

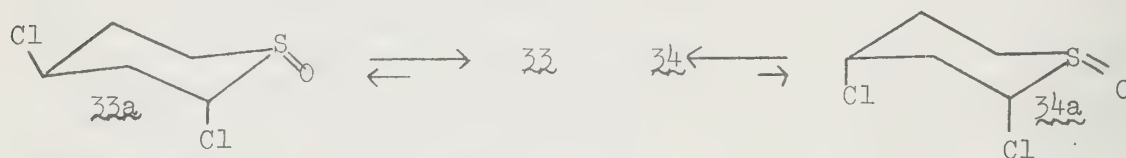
Thus, on the basis of the mechanism in Scheme 3, it is easily seen how 14, 15, 18, 19a, and 22 gave the products observed. The dideuterio-dichloro product 21b can easily be rationalized as having arisen from 19b undergoing dichlorination twice through an envelope conformation analogous to 30 and axial attack by chloride each time to give equatorial deuteriums. The fact that 85% of the monochlorinated products from the unsymmetrical sulfoxide 23 involved replacement of the hydrogen at the more highly substituted α -carbon lent additional support for an intermediate like 31, a positively charged species. If base abstraction of an α -hydrogen lead to a carbanion intermediate, chlorination would be expected to occur at the less substituted α -carbon. Thus 23 was visualized as going primarily via route two, through the boat conformation, to give 25 (from axial chloride attack) and 26 (from equatorial attack). Only traces of 27, arising from abstraction of hydrogen at the less substituted α -carbon in the boat conformation, were observed.

Product 24, also obtained from 22, was explained by having 23 go to a lesser extent via route one, equilibration of chlorosulfoxonium ions, in order for abstraction of the only α -hydrogen with favorable orientation to occur.

Other studies on the α -halogenation of various substituted thiane 1-oxides gave results consistent with the mechanism in Scheme 3. Tsuchihashi *et al.*^{20, 21} used *t*-butyl hypochlorite, sulfuryl chloride, and chlorine in the presence of potassium acetate or pyridine and N-bromosuccinimide/bromine in the presence of pyridine to obtain α -halo or α, α' -di-halo thiane 1-oxides in which the halogen atom was always introduced at a *cis*-position to the sulfinyl oxygen. For cyclic sulfoxides at least, the results were not consistent with the concerted mechanism of chlorine migration from the initially formed chlorosulfoxonium ion to the α -carbon, since *trans* products would be observed for this process. When *cis*-4-chlorothiane 1-oxide 32, the conformation of which is not completely fixed by the equatorial chlorine, was chlorinated, two products, 33 and 34, were obtained. The product 33 can be rationalized as resulting from a process analogous to route one in Scheme 3, i.e. formation of the chlorosulfoxonium ion, inversion of the sulfinyl group, *trans*-diaxial elimination of HCl, and axial attack by chloride ion to give 33a which, unlike the conformationally rigid 16, undergoes ring inversion to the more stable conformation 33. Thiane 1-oxides are known to have a strong conformational preference for the sulfoxide oxygen in the axial position.²⁵ The formation of 34 was explained



as occurring from chlorination of the other chair conformation of 32 with the sulfinyl group equatorial to give 34a which likewise underwent ring inversion to 34. When chlorinated the isomer of 32, *trans*-4-chlorothiane






1-oxide, which is less conformationally rigid than 32, gave only 33 through the process of ring inversion. Thus, when thiane 1-oxides containing small 4-substituents (e.g. *trans*-chloro,²⁰ *cis*-tosyloxy,²⁷ *trans*-hydroxy,²⁸ and *cis* or *trans*-acetoxy²⁷) which can stabilize one conformation only slightly relative to the other, the normal course of halogenation proceeds with ring inversion either before or after formation of the chlorosulfoxonium ion. For aryl or *t*-butyl groups in the 4-position, halogenation occurs with inversion of the sulfinyl group.

With iodobenzene dichloride,^{4, 6} N-chlorobenzotriazole,¹⁴ or bromine^{6c} in the presence of pyridine, α -halogenation of (R)-(+)-methyl *p*-tolyl sulfoxide afforded the corresponding (+)- α -halo sulfoxides, but in the presence of AgNO₃ the (-)-enantiomers were obtained.⁷ Conversion of both of the (-)- α -halomethyl *p*-tolyl sulfoxides to the same (-)- α -methoxymethyl *p*-tolyl sulfoxide by treatment with NaOCH₃/CH₃OH showed that both had the same absolute configuration about sulfur. One of the halogenations, either in the presence or absence of AgNO₃, must have proceeded with inver-

sion of configuration at sulfur without any breaking of the S-O bond since ¹⁸O label in the starting sulfoxide was completely retained in the α -chloro-sulfoxide when water was present.

When optically active (R)-(+)-ethyl or (R)-(+)-isopropyl p-tolyl sulfoxide was likewise halogenated, the corresponding α -halo sulfoxides were all observed to have inversion of sign of optical rotation (Table 1). Also, the

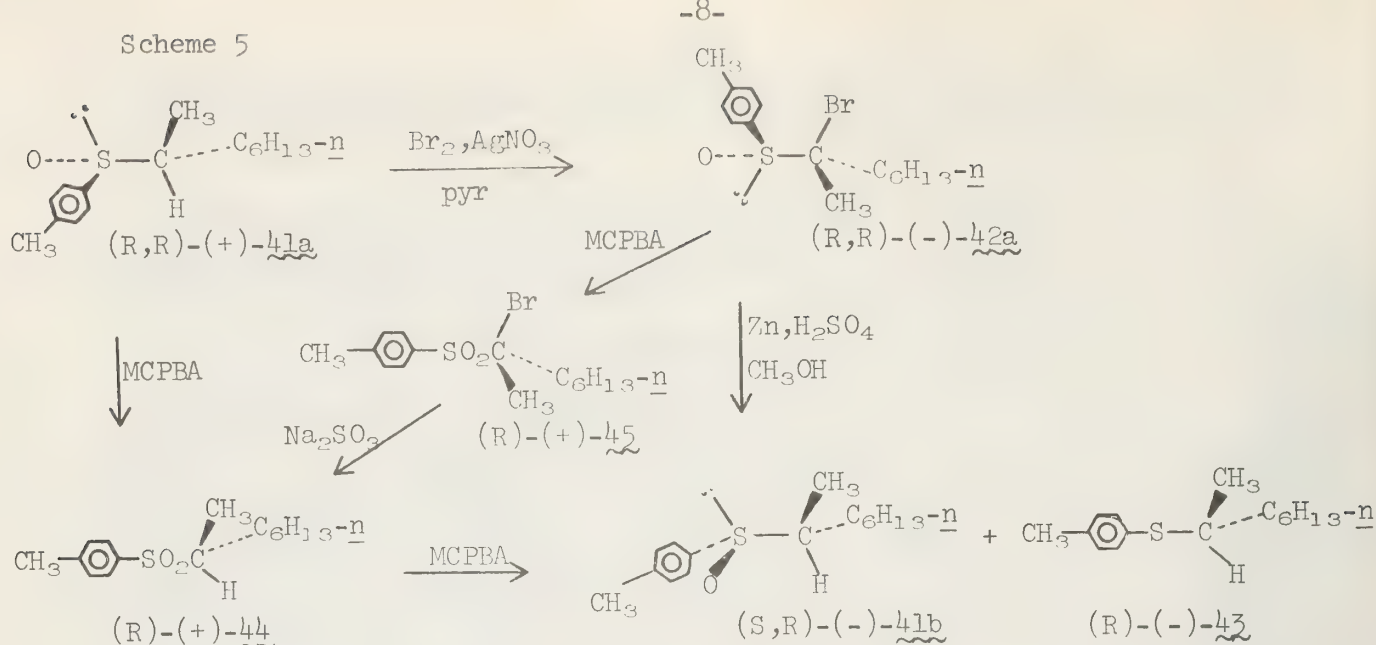
Table 1. α -Halogenation of Optically Active Sulfoxides

Sulfoxide	$[\alpha]_D^{25}$ (c 1, acetone)	α -Halo Sulfoxide $[\alpha]_D^{25}$ (c 1, acetone)			
		PhICl ₂	PhICl ₂ -AgNO ₃	Br ₂	Br ₂ -AgNO ₃
 S(O)-CH ₃	+144°	+92°	-106°	+153°(14)	-196°(99)
 S(O)-CH ₂ CH ₃	+189°	- 7°	-153°	- 83°(81)	-115°(93)
 S(O)-CH(CH ₃) ₂	+178°	-23°	-119°	- 84 (97)	-88°(100)
				(% inversion)	

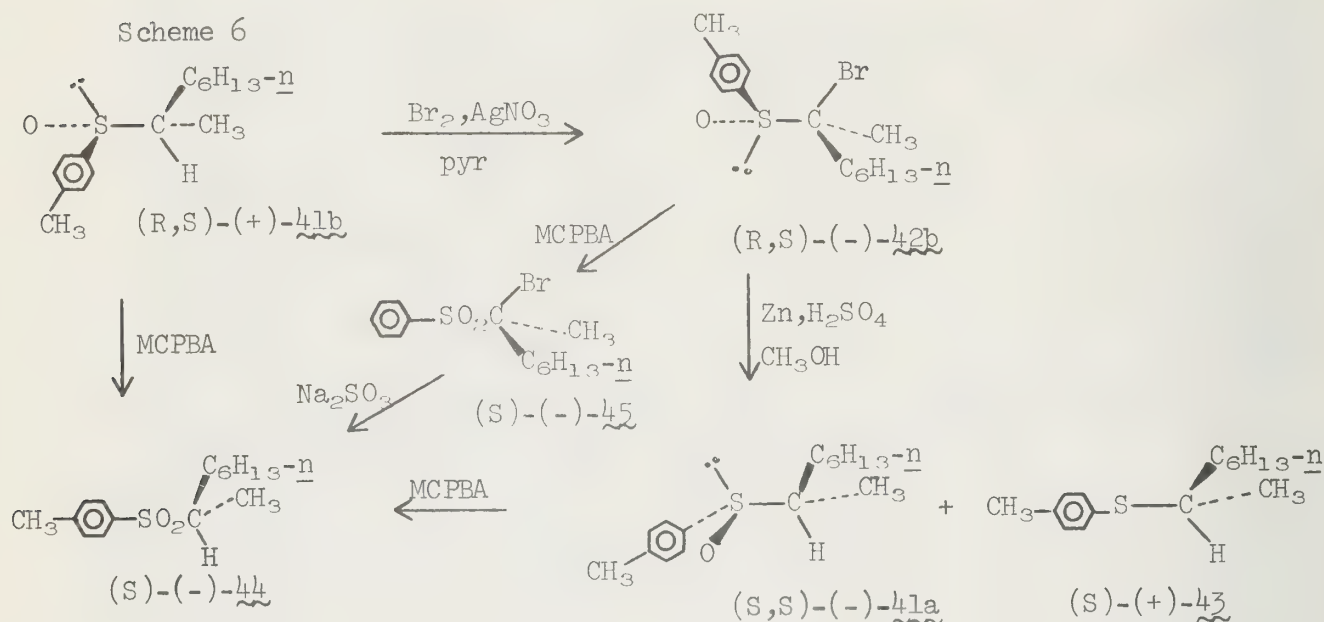
sign of the Cotton effect centered at 240-250 nm, probably due to the n- π^* transition of the sulfinyl group, in these α -halo products was opposite to that of the (+)-ethyl and (+)-isopropyl p-tolyl sulfoxides. When the (-)-bromo derivatives were dehalogenated by reduction with zinc and methanol, the resulting sulfoxides were observed to have negative specific rotations and therefore were enantiomeric to the starting ones. It was concluded that α -halogenation in these cases occurred with prevailing inversion of configuration at sulfur. Conversion of the (-)- α -chloroethyl and the (-)- α -bromoethyl p-tolyl sulfoxides to the sulfones resulted in retention of optical activity due to chirality at the α -carbon and showed that the stereochemical course at sulfur was related to the stereochemical course at carbon.^{7,19,26}

In a unique experiment that established the stereochemical courses at sulfur and the α -carbon during bromination, Montanari *et al.*²⁶ showed that in the case of acyclic sulfoxides at least, the process was concerted. When the diastereomeric (R,R)-(+)-41a and (R,S)-(+)-41b 2-octyl p-tolyl sulfoxides in Schemes 5 and 6 were brominated with Br₂/pyridine in the presence of AgNO₃ and subsequently dehalogenated by reduction with zinc and methanol, the (S,R)-(-)-41b and (S,S)-(-)-41a sulfoxides, respectively, were obtained along with the sulfides (R)-(-)-43 and (S)-(+)-43. Since the sulfoxides were enantiomers of the (+)-41b and (+)-41a starting sulfoxides, the overall process of bromination and reduction had to have been one of inversion of configuration at sulfur as expected and retention of configuration at carbon. Oxidation of (-)-41b and (-)-43 with m-chloroperbenzoic acid (MCPBA) gave the sulfone (R)-(+)-44. Likewise, the oxidation of (-)-41a and (+)-43 gave (S)-(-)-44. The sulfones were identical to those obtained from the respective oxidation of (-)-42a and (-)-42b to (+)-45 and (-)-45 and subsequent reduction with sodium sulfite. Since the stereochemistry at carbon in the α -halogenation of sulfoxides could not be determined unless the stereochemistry of the reductive dehalogenations (i.e. zinc/methanol and sodium sulfite) could be established, the oily bromo sulfoxide (-)-42b was converted to the corresponding sulfoximide so that its absolute configuration could be determined from X-ray analysis. The absolute configurations of R and S for sulfur and carbon, respectively, were found for the sulfoximide, thus establishing the stereochemical course of α -halogenation in this case to be inversion of configuration at both sulfur and carbon. The reduction dehalogenations proceeded with inversion at carbon, so that the overall process of halogenation-dehalogenation resulted in retention of configuration at carbon.

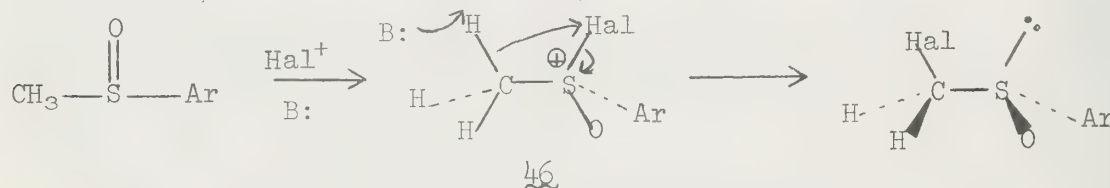
Scheme 5



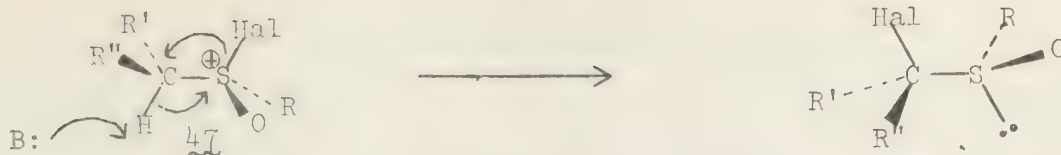
Scheme 6



A concerted mechanism previously suggested by Montanari to account for the prevailing retention of configuration at sulfur in the halogenation of methyl aryl sulfoxides in the absence of AgNO_3 ,¹⁹ required the chlorosulfoxonium ion 46 to assume a syn-periplanar conformation.



This mechanism would lead to retention of configurations at sulfur and carbon. Increasing the substitution at the α -carbon would tend to disfavor the syn-periplanar conformation for steric reasons. The experimental evidence presented, indicated that an anti-periplanar conformation 47 was more likely. A concerted abstraction of α -hydrogen and migration of halogen as anion in 47 (promoted by the presence of silver cations) explained the prevailing inversions of configuration for sulfur and α -carbon. A blending of Montanari's two concerted mechanisms also accounted for racemizations encountered in various other studies. Montanari²⁶ has concluded that the



intimate stereochemical relationship between sulfur and carbon favors a concerted mechanism, at least in the case of halogenations of acyclic sulfoxides.

On the basis of the work with thiane 1-oxides, however, a concerted intramolecular mechanism for halogenation is almost certainly ruled out. Klein and Stollar²⁷ maintain that the inverted ylide (or oxosulfenium ion) intermediate, e.g. 31, undetected as yet, can explain the stereospecificity of halogenation in acyclic sulfoxides as well. Slow rotation of the C=S bond relative to attack by halide anion would be responsible for the stereospecific attachment of halogen resulting from either nonplanarity of the inverted ylide intermediate or from electronic effects from the bent $=S(O)R$ group.

BIBLIOGRAPHY

1. M. Hojo and Z. Yoshida, *J. Amer. Chem. Soc.*, 90, 4496 (1968).
2. (a) R. Pummerer, *Chem. Ber.*, 42, 2282 (1909); (b) C. Johnson and W. Phillips, *J. Amer. Chem. Soc.*, 91, 682 (1969).
3. R. Loeppky and C. Chang, *Tet. Lett.*, 5415 (1968).
4. M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 607 (1969).
5. S. Wolfe and A. Rauk, *ibid.*, 778 (1966).
6. (a) M. Cinquini, S. Colonna, and D. Iarossi, *Boll. Sci. Fac. Chim. Ind. Bologna*, 27, 197 (1969); (b) M. Cinquini, S. Colonna, U. Folli, and F. Montanari, *ibid.*, 27, 203 (1969); (c) M. Cinquini and S. Colonna, *ibid.*, 27, 201 (1969).
7. M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 1441 (1970).
8. S. Iriuchijima and G. Tsuchihashi, *Tet. Lett.*, 5259 (1969).
9. G. Tsuchihashi and S. Iriuchijima, *Bull. Chem. Soc. Japan*, 43, 2271 (1970).
10. S. Iriuchijima and G. Tsuchihashi, *Synthesis*, 588 (1970).
11. K. Tin and T. Durst, *Tet. Lett.*, 4643 (1970).
12. G. Tsuchihashi, K. Ogura, S. Iriuchijima, and S. Tomisawa, *Synthesis*, 89 (1971).
13. T. Durst and K. Tin, *Can. J. Chem.*, 49, 2374 (1971).
14. M. Cinquini and S. Colonna, *Synthesis*, 259 (1972).
15. G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Japan*, 44, 1726 (1971).
16. M. Cinquini, S. Colonna, and D. Landini, *J. Chem. Soc., Perkin II*, 296 (1972).
17. D. Tuleen and T. Stephen, *J. Org. Chem.*, 34, 31 (1969).
18. D. Landini, F. Montanari, G. Modena, and G. Scorrano, *J. Amer. Chem. Soc.*, 92, 7168 (1970).
19. M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Chem. Soc., Perkin I*, 1886 (1972).
20. S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, 46, 921 (1973).
21. S. Iriuchijima and G. Tsuchihashi, *ibid.*, 46, 929 (1973).
22. S. Eory, R. Lett, B. Moreau, and A. Marquet, *Comp. Rend. (C)*, 1323 (1973).
23. T. Durst, K. Tin, and M. Marcil, *Can. J. Chem.*, 51, 1704 (1973).
24. F. Jung, K. Tin, and T. Durst, *Int. J. Sulfur Chem.*, 1, 1 (1973).
25. J. Martin and J. Uebel, *J. Amer. Chem. Soc.*, 86, 2936 (1964).
26. P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *ibid.*, 95, 7431 (1973).
27. J. Klein and H. Stollar, *ibid.*, 95, 7437 (1973).
28. H. Stollar and J. Klein, *J. Chem. Soc., Perkin I*, 1763 (1974).
29. J. Wicha, A. Zarecki, and M. Kocor, *Tet. Lett.*, 3635 (1973).

SYNTHESIS OF α -LINKED, cis-1,2-GLYCOSIDES
BY HALIDE ION CATALYZED REACTIONS

Reported by Jane Berlin

August 28, 1975

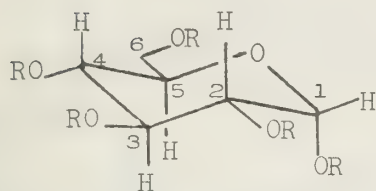
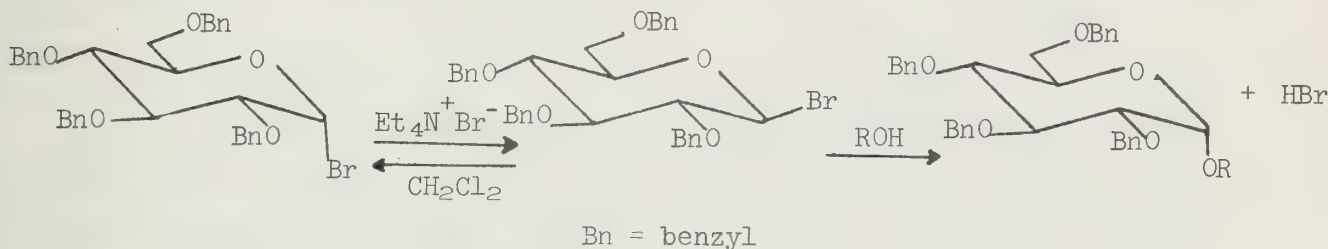


Figure 1

Synthesis of α -linked, cis-1,2-glycosides constitutes one of the classical problems of carbohydrate chemistry. Conventional substituents used as leaving groups at C-1 are electronegative and have a preferred axial configuration.^{1,2} Therefore, when non-participating groups are present on C-2 and replacement occurs with inversion, β -glycosides are the preferred product. When participating groups are present on C-2 the product is largely of trans-1,2 configuration.³ Further complications arise from the partial carbonium ion character of the intermediate, steric hindrance, and participation by groups other

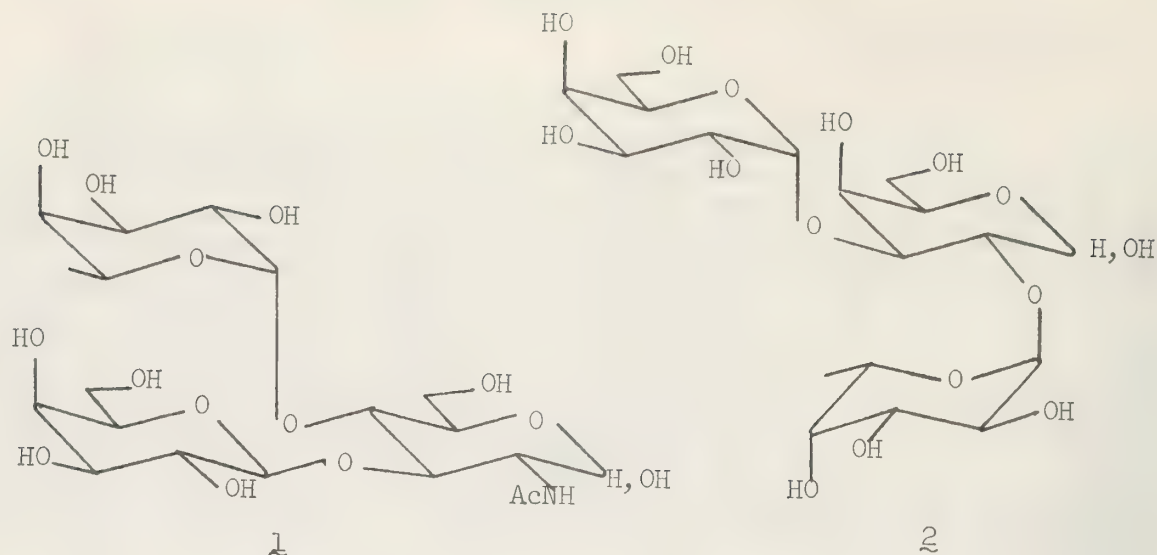
than those at C-2⁴ (Figure 1). Recent reviews⁵⁻⁷ have summarized traditional approaches to these biologically important sugars as well as some promising new methods.^{8,9}

Halide ion catalyzed glycosidation reactions were first suggested in 1968 by Lemieux,¹⁰ and independently by Ishikawa and Fletcher,¹¹ on the basis of anomerization and solvolysis studies of glycopyranosyl halides.¹²⁻¹⁷ However, only recently have details of the reaction and its applications to the synthesis of disaccharides and oligosaccharides been published.¹⁷⁻²⁰ In halide ion catalyzed glycosidations, an α -glycosyl halide, substituted at the 2-position with a non-participating group, is converted to the less stable β -glycosyl halide which then reacts, at a much greater rate than the α -anomer, with the alcohol or sugar to give predominantly α -cis-1,2-glycosidic linkages.



High yields of α -glycosides can be effected by carrying out the reaction at room temperature in benzene or methylene chloride and using excess glycosyl halide. Although addition of base does not catalyze the glycosidation reaction,¹⁸ addition of activated 4 Å molecular sieves as an acid acceptor has been effective in preventing acetyl group migration in certain protected sugars.²⁰

Lemieux and co-workers have applied this method to the synthesis of blood-group antigenic determinants. Bromide ion catalyzed reaction of tri-O-benzyl-L-fucopyranosyl bromide with 2,2,2-trichloroethyl 2-acetamido-6-O-acetyl-3-O-(tetra-O-acetyl- β -D-galactopyranosyl)-2-deoxy- β -D-glycopyranose provided the protected derivative of the Lewis a blood-group substance (1) in 80% yield.¹⁹ Similarly, the terminal structure of the blood-group B antigenic determinant (2), which contains two α -cis-1,2-glycosidic linkages, has been synthesized.²⁰



The success achieved in the synthesis of oligosaccharides using halide ion catalyzed glycosidation reactions augurs well for a capability to approach through synthesis important biological²² and chemical problems involving carbohydrates.

BIBLIOGRAPHY

1. R. U. Lemieux and S. Koto, *Tetrahedron*, 30, 1933 (1974).
2. R. U. Lemieux in "Molecular Rearrangements," Vol. II, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 12.
3. A. C. West and C. Schuerch, *J. Amer. Chem. Soc.*, 95, 1333 (1973).
4. J. M. Fréchet and C. Schuerch, *J. Amer. Chem. Soc.*, 94, 604 (1972).
5. C. Schuerch, *Accts. Chem. Res.*, 6, 184 (1973).
6. G. Wulff and G. Röhle, *Angew. Chem., Int. Ed. Engl.*, 13, 157 (1974).
7. B. Fraser-Reid, *Accts. Chem. Res.*, 8, 192 (1975).
8. D. E. Iley and B. Fraser-Reid, *J. Amer. Chem. Soc.*, 97, 2563 (1975).
9. R. U. Lemieux, K. James and T. L. Nagabhushan, *Can. J. Chem.*, 51, 42 (1973).
10. R. U. Lemieux, Gordon Research Conference, The Chemistry of Carbohydrates, Tilton, N. H., June 10-14, 1968.
11. T. Ishikawa and H. G. Fletcher, Jr., *J. Org. Chem.*, 34, 563 (1969).
12. A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 4637 (1960).
13. R. U. Lemieux and A. R. Morgan, *J. Amer. Chem. Soc.*, 85, 1889 (1963).
14. R. U. Lemieux and D. R. Lineback, *Can. J. Chem.*, 43, 94 (1965).
15. R. U. Lemieux and J. Hayami, *Can. J. Chem.*, 43, 2162 (1965).
16. R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, 43, 2214 (1965).
17. R. U. Lemieux and G. Huber, *Can. J. Chem.*, 33, 128 (1955).
18. R. U. Lemieux, K. B. Hendriks, R. V. Stick and K. James, *J. Amer. Chem. Soc.*, 97, 4056 (1975).
19. R. U. Lemieux and H. Driguez, *J. Amer. Chem. Soc.*, 97, 4063 (1975).
20. R. U. Lemieux and H. Driguez, *J. Amer. Chem. Soc.*, 97, 4069 (1975).
21. P. A. Gent and R. Gigg, *J. Chem. Soc., Perkin Trans. I*, 1446 (1974).
22. R. U. Lemieux, D. R. Bundle and D. A. Baker, *J. Amer. Chem. Soc.*, 97, 4076 (1975).

NUCLEOPHILIC RING OPENINGS OF ACTIVATED CYCLOPROPANES

Reported by Brian N. Holmes

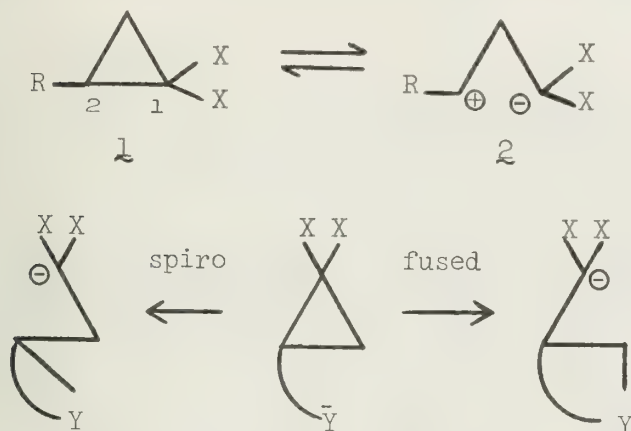
September 4, 1975

The propensity of doubly activated cyclopropanes to undergo cleavage upon treatment with nucleophiles has been recognized since the studies of Bone and Perkin.¹ This seminar will deal with the mechanism and synthetic applications of nucleophilic cyclopropane ring openings.

MECHANISM

Studies of cyclopropanes substituted at C₁ with two carbanion-stabilizing substituents and at C₂ with a cation-stabilizing substituent have demonstrated that reversible C₁-C₂ bond cleavage to zwitterions precedes nucleophilic attack

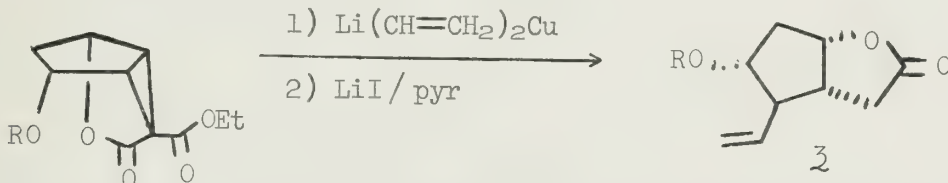
in some cases (1→2).² In general, nucleophilic attack occurs at the center most able to stabilize positive charge,³ and intramolecular attack occurs preferentially by a spiro rather than fused mode.⁴ Cyclic acylals are particularly good activating functions for these reactions since both ester planes are held in a conformation orthogonal to the emerging carbanion.⁵ Although most nucleophilic cyclopropane cleavages appear to proceed through intermediates with zwitterionic character, more highly strained



systems (e.g., quadracycline derivatives) undergo cleavages that are interpreted as S_N² processes.⁶

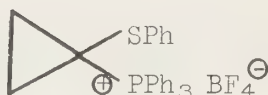
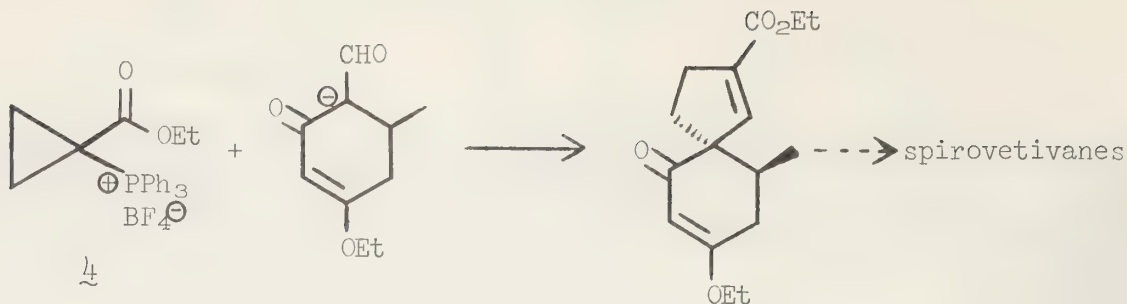
SYNTHETIC APPLICATIONS

Doubly activated cyclopropanes are used to effect homoconjugate addition. Cyclopropyl malonic esters have been used to prepare furanoid systems,⁷ pyrrolizidines, indolizidines⁸ and carbocyclic systems.⁹ Corey used a nucleophilic cyclopropane ring opening to control stereochemistry in the synthesis of the prostanoid 3.¹⁰ While most nucleophiles add in a 1,5 manner to activated



vinylcyclopropanes, sulfides,¹¹ enamines,¹² and lithium dialkylcopper¹³ reagents add in a 1,7 manner.

Carboethoxycyclopropyltriphenylphosphonium fluoroborate (4) was designed to effect cycloalkenylation of carbonyl compounds.¹⁴ Dauben has recently reported a highly efficient general synthetic scheme for spirovetivanes using 4 in the key transformation.¹⁵ A similar reagent, 5, has been used to synthesize substituted cyclopentanes.¹⁶



The scope of nucleophilic cyclopropane ring opening is an active area of research and holds considerable synthetic promise.

BIBLIOGRAPHY

1. a) W. A. Bone and W. H. Perkin, *J. Chem. Soc.*, 67, 108 (1895); b) R. H. Best and J. F. Thorpe, *J. Chem. Soc.*, 685 (1909); c) R. W. Kierstead, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 3610 (1952); d) W. E. Truce and L. B. Lindy, *J. Org. Chem.*, 26, 1463 (1961); e) J. M. Stewart and H. H. Westberg, *J. Org. Chem.*, 30, 1951 (1965).
2. a) E. W. Yankee and D. J. Cram, *J. Amer. Chem. Soc.*, 92, 6328, 6329, 6331 (1972); b) E. W. Yankee, R. D. Badea, N. E. Howe, and D. J. Cram, *J. Amer. Chem. Soc.*, 95, 4210 (1973); c) E. W. Yankee, B. Spencer, N. E. Howe and D. J. Cram, *J. Amer. Chem. Soc.*, 95, 4220 (1973); d) N. E. Howe, E. W. Yankee, and D. J. Cram, *J. Amer. Chem. Soc.*, 95, 4230 (1973); e) A. B. Chmurny and D. J. Cram, *J. Amer. Chem. Soc.*, 95, 4237 (1973).
3. S. Danishefsky and G. Rovnyak, *J. Org. Chem.*, 40, 114 (1975).
4. a) S. Danishefsky, J. Dynak, E. Hatch, and Y. Yamamoto, *J. Amer. Chem. Soc.*, 96, 1256 (1973); b) S. Danishefsky, J. Dynak, Y. Yamamoto, *J. C. S. Chem. Comm.*, 81 (1973).
5. S. Danishefsky and R. K. Singh, *J. Amer. Chem. Soc.*, 97, 3239 (1975).
6. a) G. F. Koser and S.-M. Yu, *J. Org. Chem.*, 38, 1755 (1973); b) S. F. Nelsen and J. C. Calabrese, *J. Amer. Chem. Soc.*, 95, 8385 (1973).
7. a) S. Danishefsky, S. J. Etheredge, J. Dynak and P. McCurry, *J. Org. Chem.*, 39, 2658 (1974); b) S. Danishefsky and J. Dynak, *Tetrahedron Lett.*, 79 (1975).
8. S. Danishefsky and J. Dynak, *J. Org. Chem.*, 39, 1979 (1974).
9. a) J. E. Dolfini, K. Menich and P. Corlin, *Tetrahedron Lett.*, 4421 (1966); b) N. A. Abraham, *Tetrahedron Lett.*, 451 (1973); c) N. A. Abraham, *Tetrahedron Lett.*, 1393 (1974); d) S. Danishefsky, M. Y. Tsai and J. Dynak, *J. C. S. Chem. Comm.*, 7 (1975).
10. E. J. Corey, and P. L. Fuchs, *J. Amer. Chem. Soc.*, 94, 4014 (1972).
11. S. Danishefsky and G. Rovnyak, *J. C. S. Chem. Comm.*, 820 (1972).
12. S. Danishefsky and G. Rovnyak, *J. C. S. Chem. Comm.*, 636 (1969).
13. a) G. Daviand and P. Miginak, *Tetrahedron Lett.*, 977 (1972); b) P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, 38, 2100 (1973).
14. P. L. Fuchs, *J. Amer. Chem. Soc.*, 96, 1607 (1974).
15. W. G. Dauben and D. J. Hart, *J. Amer. Chem. Soc.*, 97, 1622 (1975).
16. J. P. Marino and R. Landich, Abstract of Paper, 170th National ACS Meeting, Chicago, Ill., (1975).

AMINOCYCLITOL ANTIBIOTICS: PREPARATION OF ANALOGUES

Reported by H. Mitchell Rubenstein

September 8, 1975

Although neomycin B,¹ a broad spectrum aminocyclitol antibiotic, has found wide use in the agricultural industry, its medicinal use has been limited by its ototoxicity² and nephrotoxicity² when administered to patients. In addition, the occurrence of bacteria resistant³ to neomycin B has necessitated modification of the antibiotic.

Semi-synthetic preparation (chemical modification of the parent antibiotic) of improved chemotherapeutic compounds from cephalosporin,⁴ rifamycin,⁵ penicillin,⁶ tetracycline,⁷ and lincomycin⁸ has been accomplished successfully. However, the aminocyclitol antibiotics, due to their complex structures, have not lent themselves to successful preparation of improved antibiotics by this method.

Alternatively, a modification can be achieved by the total synthesis of an antibiotic. This approach has been successfully applied to many members of the aminocyclitol antibiotics;⁹ however, the total synthesis of neomycin B has not been accomplished, although a component, neamine,^{10a} has been synthesized. Since the aminocyclitol antibiotics consist of subunits, analogues can be made by preparing the desired modification in a subunit and then substituting this subunit analogue in the total synthesis of the antibiotic. This has been accomplished for neamine,^{9,10a,10b} and ribostamycin,¹¹ among others.⁹ This method has shown promise for determining the effect of modification on biological activity; however, the conversion to large scale production for marketing may be difficult.

Another approach has been to use biological methods to alter the antibiotic. One method utilized additions in the organism's diet. In this way, side chain modification in penicillin,⁶ substitution of methyl proline isomers in actinomycin,¹² substitution of the chromophore group in quinomycin,¹³ and the substitution of bromine for chlorine in 7-chlorotetracycline¹⁴ have been accomplished. The obvious disadvantage to this method has been the separation problem which occurs since the parent antibiotic is usually also present. A second method is based on microbial transformation of intact antibiotics. Although this process is usually harmful³ to the biological activity of an antibiotic (aminocyclitols), there has been success with lincomycin¹⁵ and the related clindomycin.¹⁶ A third approach was introduced by Rinehart and Shier.¹⁷ Since it has been shown that deoxystreptamine (the aminocyclitol moiety) is incorporated directly into neomycin¹⁸, it should be possible to find a mutant incapable of forming deoxystreptamine, but able to form antibiotic when fed deoxystreptamine. Rinehart and Shier found such a mutant.¹⁹ This new technique could now be utilized to prepare neomycin analogues (hybrimycins¹⁷), modified in the aminocyclitol moiety, if the deoxystreptamine analogue chosen was suitable for incorporation. The requirements for incorporation of an analogue are that it can permeate the cell wall and can be utilized by the proper enzymes as a substrate. In addition, the analogue formed must have biological activity. Rinehart and Shier²⁰ fed 29 deoxystreptamine analogues, two of which (streptamine and epistreptamine) were successfully converted to hybrimycins,¹⁷ indicating that only modifications at position C-2 were successful.³ There also appeared to be a strict requirement for two underivatized amino groups which were situated meta to each other in a cis conformation. Modification or substitution of the hydroxyl groups at position C-5, or C-6 of deoxystreptamine were unsuccessful in bioconversion to hybrimycins.

Mutants for streptomycin,²¹ ribostamycin,²² paromomycin,²⁰ and kanamycin^{20,22} have also been isolated. Analogues have been prepared from some of these mutants. The results that have come from ribostamycin (an aminocyclitol antibiotic and a large portion of neomycin) are particularly interesting. Kojima and Satoh²² have shown that their mutant also converted streptamine and epistreptamine to active compounds, however, a third deoxy-streptamine analogue 1-N-methyl deoxystreptamine was also incorporated. In addition, the mutant accepted neamine and a neamine analogue as precursors to ribostamycin and a ribostamycin analogue, respectively. These results have clearly indicated that a reinvestigation of the supposed requirement of a free amino group at position C-1 and a free hydroxyl group at position C-4 is necessary. Four dideoxystreptamine compounds recently prepared²³ should also be examined.

The approach introduced by Rinehart and Shier has been expanded to other antibiotics in the aminocyclitol group of antibiotics. The ability to prepare hybriamycins quickly and the commercial feasibility of large scale production of useful analogues by fermentation makes this method very attractive.

BIBLIOGRAPHY

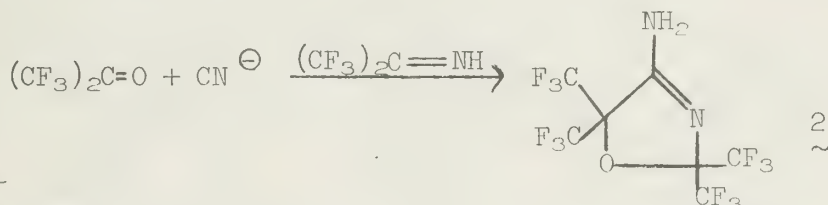
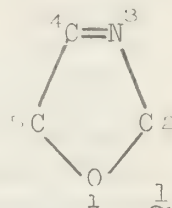
1. K. L. Rinehart, Jr., *The Neomycins and Related Antibiotics*, John Wiley and Sons, Inc., New York, 1964.
2. J. E. Hawkins, Jr., in *Neomycin, Its Nature and Practical Application*, S. A. Waksman, ed., Williams and Wilkins Co., Baltimore, 1958, chap 11.
3. O. K. Sebek, *Lloydia*, 37, 117 (1974); H. Umezawa, in *Advances in Carbohydrate Chemistry and Biochemistry*, Vol. 30, R. S. Tipson & D. Horton, ed., Academic Press, New York, 1974, p 183.
4. E. W. Flynn, *Antimicrob. Ag. Chemother.* 1966, 715 (1967).
5. P. Sensi, N. Maggi, S. Furesz, and G. Maffh, *ibid.*, 1966, 699 (1967).
6. K. E. Price, A. Gourevitch, L. C. Cheney, *ibid.*, 1966, 670 (1967).
7. D. L. J. Clive, *Quart. Rev.*, 22, 435 (1968).
8. B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *Antimicrob. Ag. Chemother.* 1966, 727 (1967).
9. S. Umezawa, in *Advances in Carbohydrate Chemistry and Biochemistry*, Vol. 30, R. S. Tipson & D. Horton, ed., Academic Press, New York, 1974, and literature cited therein.
10. a) S. Umezawa, K. Tatsuta, T. Tsuchiya, and E. Kitazawa, *J. Antibiotics* A20, 53 (67); b) T. Suami, private communication.
11. S. Umezawa, T. Tsuchiya, D. Ikeda, and H. Umezawa, *J. Antibiotics*, 25, 613 (1972).
12. T. Yoshida, A. Mauger, H. Weissbach, and E. Katz, *J. Bacteriol.*, 95, 952 (1968).
13. T. Yoshida, Y. Kimura, and H. Katagiri, *J. Antibiotics*, 21, 465 (1968).
14. P. Sensi, G. A. de Ferrari, G. G. Gallo, and G. Rolland, *Angew. Chem.*, 68, 166 (1956).
15. A. D. Argoudelis and D. J. Mason, *J. Antibiotics*, 22, 289 (1969).
16. A. D. Argoudelis, J. H. Coats, D. J. Mason, and O. K. Sebek, *J. Antibiotics*, 22, 309 (1969).
17. W. T. Shier, Ph.D. Thesis, University of Illinois, 1970.
18. F. C. Falkner, Ph.D. Thesis, University of Illinois, 1969.
19. W. T. Shier, K. L. Rinehart, Jr., and D. Gottlieb, *Proc. Nat. Acad. Sci. (U.S.)*, 63, 198 (1969).
20. W. T. Shier, S. Ogawa, M. Hichens, and K. L. Rinehart, Jr., *J. Antibiotics*, 26, 551 (1973); W. T. Shier, P. C. Schaefer, D. Gottlieb, and K. L. Rinehart, Jr., *Biochemistry*, 13, 5075 (1974).
21. K. Nagaoka and A. L. Demain, *Bacteriological Proc.*, 19 (1974).
22. M. Kojima and A. Satoh, *J. Antibiotics*, 26, 784 (1973).
23. T. Suami, S. Ogawa, H. Uchino, and Y. Funaki, *J. Org. Chem.*, 40, 456 (1975).

THE PHOTOCHEMICAL SYNTHESIS OF 3-OXAZOLINES

Reported by David House

September 25, 1975

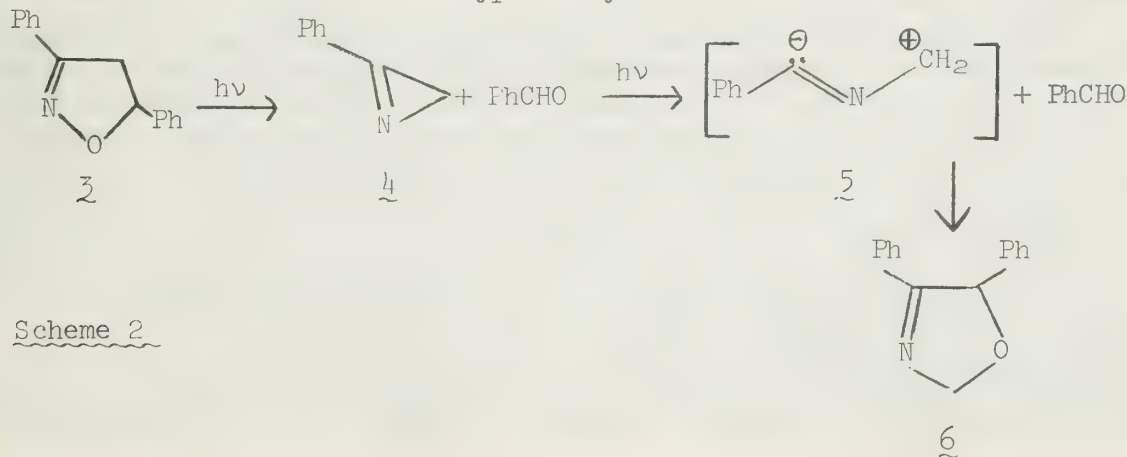
3-Oxazolines are five-membered heterocyclic compounds which have a double bond in the 3-position 1. The first 3-oxazoline was reported by German workers in 1932.¹ Several different 3-oxazolines were prepared by condensing the amides of several acids (e.g. lactic acid) with acetone and HCl, then treating these products with MeI—Ag₂O to yield the oxazolines. Since this initial report, 3-oxazolines have been included in two major review articles.^{2,3} These compounds, which are rare in comparison with 2-oxazolines, have been mainly limited to the research laboratory, and only one example of a naturally occurring 3-oxazoline has been confirmed.⁴ Most of the early syntheses of 3-oxazolines utilized traditional wet chemical methods. A representative example of the thermal preparation of a 3-oxazoline (in 37% yield) is that given by W. J. Middleton, D. Metzgen, K. B. Cunningham, and C. G. Krespan in the synthesis of 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline 2⁵ as outlined in Scheme 1. Hexafluoroacetone was treated with sodium cyanide in acetonitrile, and then hexafluoroacetone imine.

Scheme 1

Since the publication of an article by H. Giezendanner, M. Märky, B. Jackson, H. -J. Hansen, and H. Schmid in 1972,⁶ almost all articles concerning 3-oxazolines have dealt with the photochemical reactions. This abstract is concerned with the photochemical syntheses and properties of 3-oxazolines.

Isoxazolines and Aldehydes

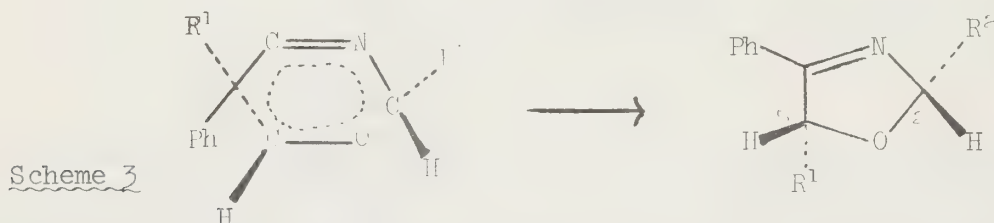
In a preliminary communication on photochemical reactions of azirines,⁵ it was reported that the irradiation of 3,5-diphenyl-2-isoxazoline 3 in benzene gave 4,5-diphenyl-3-oxazoline 6 (Scheme 2) and β -amino-chalcone in 7% and 5% yields, respectively. The isoxazoline was irradiated in the presence of [¹⁴C] --labelled benzaldehyde to discern the reaction route, and the labelled 3-oxazoline was isolated. The rationale hypothesized a photochemical decomposition of the isoxazoline into 3-phenyl-2H-azirine 4 and benzaldehyde. The photochemical ring opening of the azirine would yield the 1,3-dipole, benzonitrile methylene ylide 5, and this would add thermally, in a regiospecific manner, to benzaldehyde in a ground state cycloaddition to form the oxazoline. This type of cycloaddition was a known reaction. When

Scheme 2

the 3-phenyl-2H-azirine in benzene was irradiated in the presence of an equimolar amount of benzaldehyde, the oxazoline was obtained in 62% yield. The hydrolysis of the oxazoline gave benzoin, which proved the proposed structure to be correct. This cycloaddition was repeated with several substituted aldehydes and azirines and found to be a general type of reaction. Structures were confirmed by independent syntheses. Another possible route proceeding through styrene oxide and the aryl cyanide was subsequently eliminated when styrene oxide and the aryl cyanide in benzene were irradiated and no oxazoline was formed.⁷

Most of the photochemical reactions have used substituted azirines with appropriate substrates as starting materials. Concerning the azirine component, the electronically excited singlet state of the azirine opens to give what is apparently the singlet ylide,⁸ and this 1,3-dipole ylide has been observed in a matrix of 2,2-dimethylbutane and pentane (8:3) at -185°C via ultraviolet spectroscopy.⁹

Where cis and trans isomers are possible, the cycloaddition favors the cis-configuration. This has been explained in that the 1,3-dipolar addition is kinetically controlled, and the ylide assumes a transoid conformation.¹⁰ In Scheme 3, the aldehyde reacts in such a way as to minimize the interaction between R' and the phenyl on C3. The stereoisomeric 3-oxazolines are

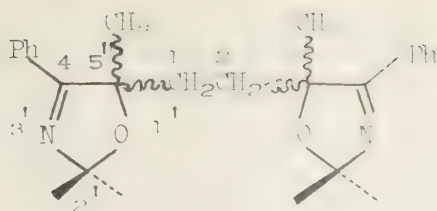


distinguishable by nmr spectra by the homoallylic coupling constants between the hydrogen atoms on C2 and C5.

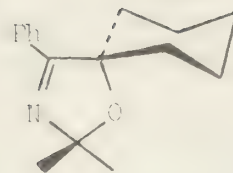
The cycloaddition is very dependent upon electronic effects.¹¹ Illustrating this, 3-phenyl-2H-azirine and 2,3-diphenyl-2H-azirine do not react readily with acetone or acetophenone, but in the presence of trifluoromethyl ketone or diethyl mesoxalate (where the C=O bonds are more polarized) yields of 3-oxazoline of 30% to 60% are obtained. Even the C=O group in esters may react if activated by a neighboring electron acceptor. For example, 1-cyanoethyl formate reacts with 2,3-diphenyl-2H-azirine to yield 5-cyano-2,4-diphenyl-5-ethoxy-3-oxazoline (cis and trans, 30% total yield). The nitrile addition product is also found in 14% yield. This reaction is considered in more detail further into the abstract.

Ketones

Ketones have also been found to give 3-oxazolines upon cycloaddition with the benzonitrile-methylides, and high yields have been obtained using activated ketones (e.g. R = CF₃, benzophenone); though, in general, aldehydes react more rapidly than the ketones. The ketones show the same regioselectivity as aldehydes. Equimolar amounts or excesses of ketones are needed to avoid excessive side reactions, for example, when 2H-azirine was irradiated with only 0.5 mol-equivalent of acetonylacetone, the 3-oxazoline bis-addition product **7** was obtained in 74% yield (2:1 mixture of racemic:meso forms).¹² Spiro compounds have been obtained by using certain cyclic ketones such as cyclohexanone and cyclopentanone. When irradiated with cyclohexanone, 3-phenyl-2,2-dimethyl-azirine formed cyclohexanespiro-5' (2',2'-dimethyl-4'-phenyl-3'-oxazoline) **8** in 86% yield; irradiation in the presence of cyclopentanone led to the spiro-(3-oxazoline) and (but-3'-en-yl)-2,2-dimethyl-4-

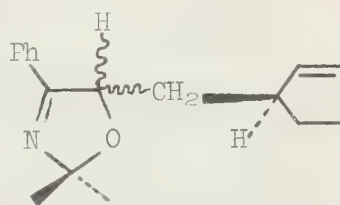


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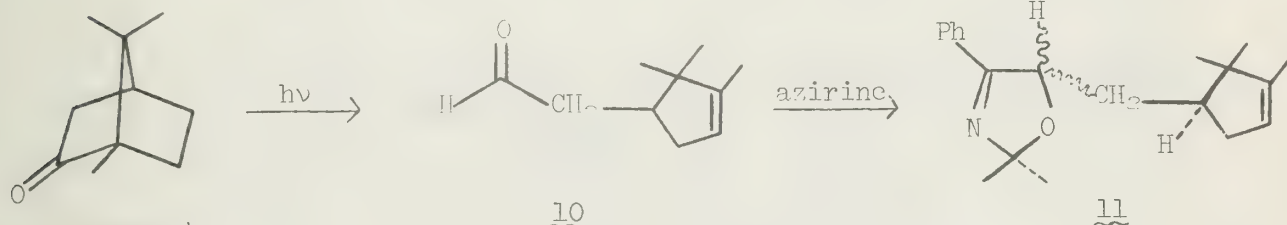


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phenyl-3-oxazoline in a 4:1 ratio (51.4% total yield). The latter product was formed by a known reaction which proceeds through a 4-pentenal intermediate. The percent yield of the latter product could be increased to about 80% if the cyclopentanone was first irradiated and the azirine subsequently added. Irradiation of azirines with bridged ketones has also been found to yield 3-oxazolines. Illustrative of this is the reaction of norcamphor and 2,2-dimethyl-3-phenyl-azirine to yield a stereoisomeric mixture of 5- Δ^3 -cyclopentenylmethyl-2,2-dimethyl-4-phenyl-3-oxazoline 9 (1:1 ratio, 55% total yield). None of the spiro adduct was formed. The bridged ketone was found to proceed via the aldehyde intermediate, Δ^2 -cyclopentenyl-acetaldehyde, and irradiation of the aldehyde and the azirine gave the 3-oxazoline in 83% yield. The rearrangement of the bridged ketone was illustrated by using d,l-camphor and observing the aldehyde intermediate 10 and the 3-oxazoline products 11 and is shown in Scheme 4.



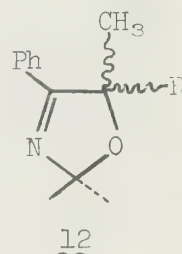
9



Scheme 4

α -Keto-esters have been irradiated with azirines to yield 3-oxazolines in low to moderate yields.¹² In this case, the ester carbonyl group also reacts but to a lesser extent. For example, the irradiation of 3-phenyl-2,2-dimethyl-azirine and the ethyl ester of pyruvic acid in benzene yielded the 5-ethoxycarbonyl-2,2,5-trimethyl-4-phenyl-3-oxazoline 12 (where R is $\text{CO}_2\text{CH}_2\text{CH}_3$) in 20.9% yield. The by-product, 5-acetyl-5-ethoxy-2,2-dimethyl-4-phenyl-3-oxazoline, gave 5-acetyl-5-hydroxy-2,2-dimethyl-4-phenyl-3-oxazoline in 5.7% yield upon purification by column chromatography using silica gel.

β -Keto-esters and the usual ylides arising from the irradiation of azirines also form the expected 3-oxazolines.¹² Illustrative of this is the photochemical reaction of 3-phenyl-2,2-dimethyl-azirine with acetoacetic ester yielding the 5-ethoxycarbonylmethyl-2,2,5-trimethyl-4-phenyl-3-oxazoline 12 (where R is $\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$) in 25% yield.

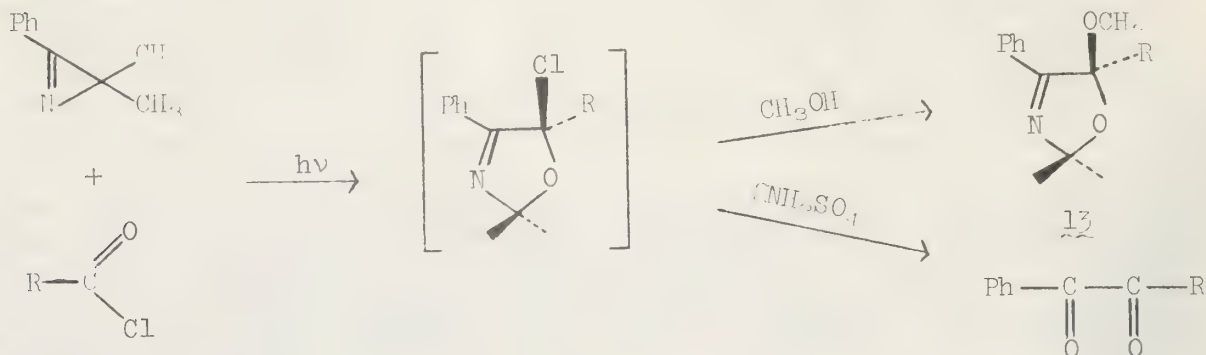


12

Acid Chlorides and Anhydrides

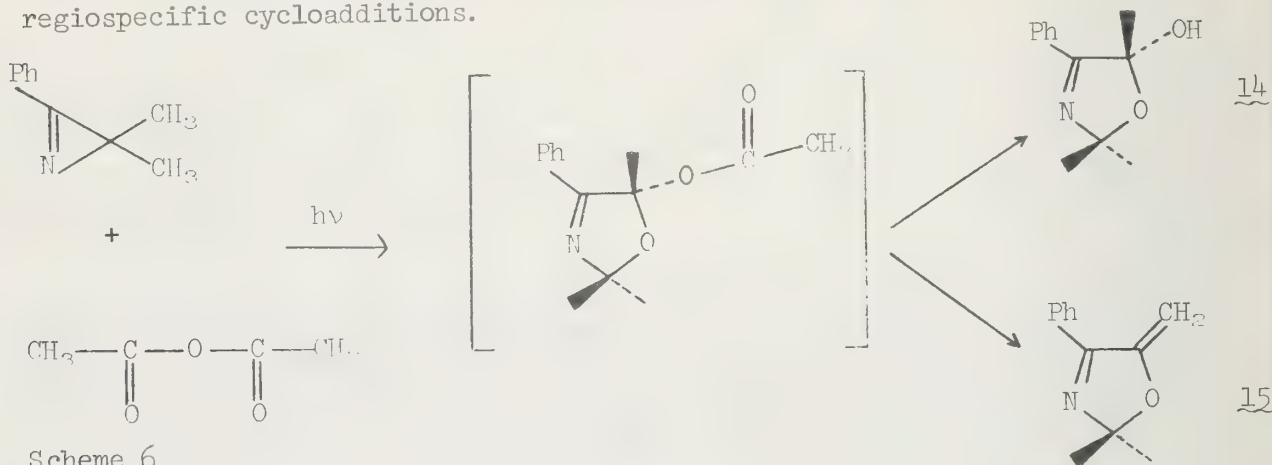
If 2,3-diphenyl-2H-azirine is irradiated in the presence of acid chlorides, oxazoles may be obtained in moderate yields.¹³ When 2,2-dimethyl-3-phenyl-azirine was irradiated under the same conditions, 5-methoxy-2,2-dimethyl-4-phenyl-3-oxazolines 13 were obtained in moderate yields after methanolysis as in

Scheme 5. A side product was the diketone, which was isolated in low yield, which increased significantly upon addition of 2N H₂SO₄. These data suggest that the oxazole reaction proceeds through a 5-chloro-2,4,5-phenyl-3-oxazoline intermediate, which loses HCl in the presence of NEt₃ to form the substituted



oxazole; however, no intermediate could be isolated. The 5-methoxy-2,2-dimethyl-4-phenyl-3-oxazoline were obtained where R on C5 was phenyl, C₆H₄-4-F, C₆H₄-4-OCH₃, and C(CH₃)₃.

An analogous case with the acid chlorides is that of anhydrides.¹³ The irradiation of 2,2-dimethyl-3-phenyl-azirine with acetic acid anhydride yields, via the 5-acetoxy-3-oxazoline intermediate, 5-hydroxy-2,2,5-trimethyl-4-phenyl-3-oxazoline 14 and 2,2-dimethyl-5-methyliden-4-phenyl-3-oxazoline 15 as shown in Scheme 6. Again, the intermediate could not be isolated, but the formation of the 3-oxazolines is consistent with the previous regiospecific cycloadditions.

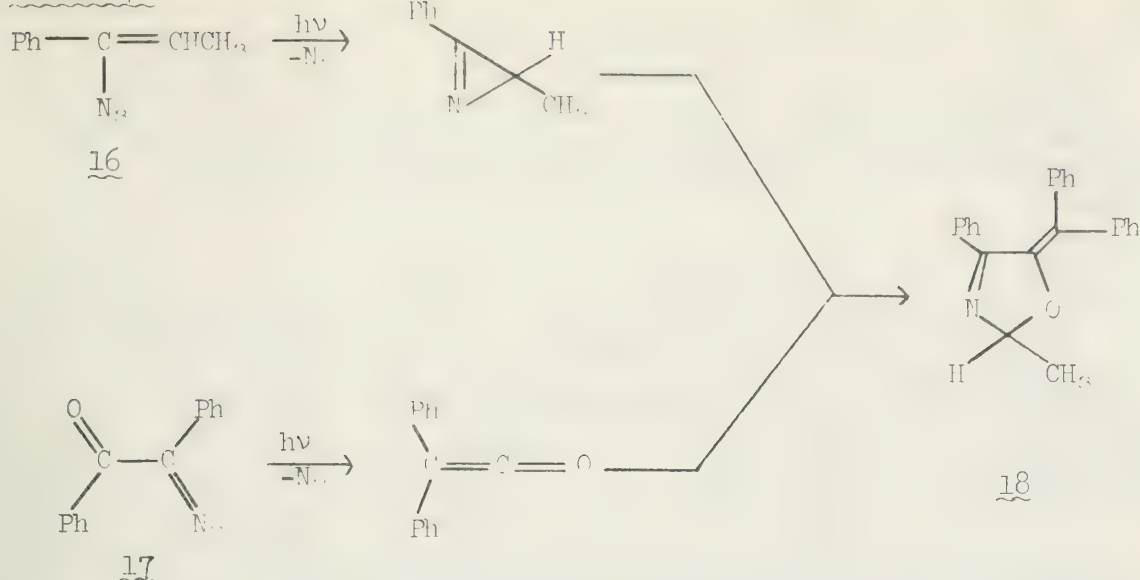


Multiple Double Bonds

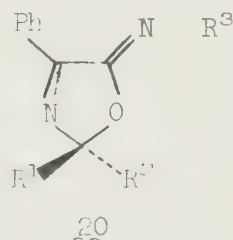
The photochemical reactions of azirines (phenylazirines in particular) with substrates containing cumulative double bonds is also general in nature. Perhaps the most obvious case is that of ketenes.¹⁴ The irradiation of certain substituted azirines in the presence of ketene yields the substituted 5-methylen-3-oxazoline in about 20% yield. The adduct 2-methyl-4-phenyl-5-diphenylmethylen-3-oxazoline 18 was formed in about 30% preparative yield from the irradiation of α -azidopropenylbenzene 16 and azibenzile 17 as represented in Scheme 7. Adducts were also obtained with other substituted phenylazirines.

When carbon dioxide is vigorously bubbled through an irradiated sample of phenylazirine, the corresponding substituted 4-phenyl-3-oxazolin-5-one 19 is obtained in yields of about 70% when C2 is substituted with H, CH₃, and phenyl combinations. In a low temperature experiment using a 2,2-dimethylbutane--pentane (8:3) matrix, 2,2,4-triphenyl-3-oxazolin-5-one

Scheme 7



eliminated carbon dioxide when irradiated at 250 to 350 nm at -190°C to give the corresponding ylide. Based on UV data, the ylide from the oxazoline recombined to a considerable extent with the carbon dioxide trapped in the



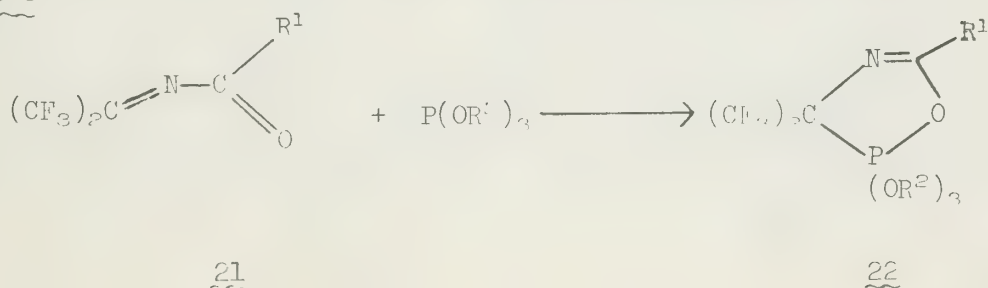
matrix to yield the starting oxazolinone. Further irradiation of the matrix at 366 nm at -185°C produced the 2,2,3-triphenylazirine.⁹ The oxazolinones may be reacted further; as exemplified by the irradiation of 4-benzyl-3-oxazolin-5-one with methyl trifluoroacetate in pentane to yield 4-benzyl-5-methoxy-5-trifluoromethyl-3-oxazoline and carbon dioxide.¹⁵

Isocyanates have also been used as substrates, and it is the $\text{C}=\text{O}$ bond and not the $\text{C}=\text{N}$ bond which reacts to give the cycloaddition product 20.¹⁵ Examples of substituted phenylazirines irradiated in the presence of isocyanates were carried out where, for the oxazoline, C2 was substituted with CH_3 , CH_3 , and CH_3 , phenyl, and the R group of the isocyanate was phenyl and *o*-tolyl, respectively. Yields were between 33% and 45%, and irradiation was on the order of 4 to 15 hours.

Phosphonates

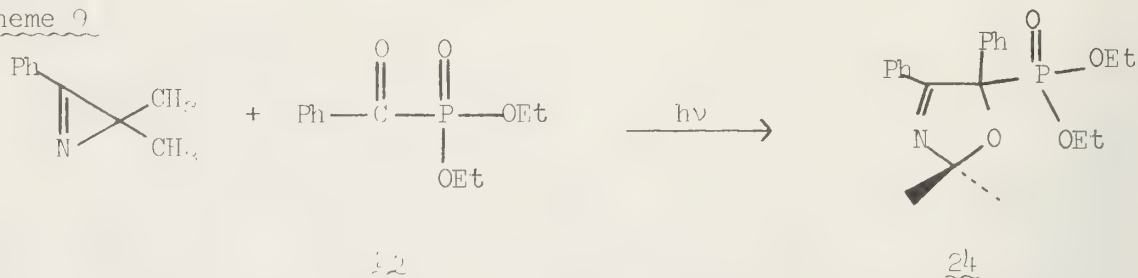
Phosphonates as substrates were first used by N. Gakis, H. Heimgartner, and H. Schmid¹⁷ who irradiated dimethylazirines in the presence of dimethyl phosphonate and diethylbenzyl phosphonate. This reaction was reminiscent of the reaction of 1,1,1,3,3,3-hexafluoro-2-(acylimino)propanes 21 with phosphites which yields 4,5-dihydro-1,3,5P^V-oxazaphospholes 22 as in Scheme 8.

Scheme 8



Upon heating, the oxazaphospholes fragment to form $\text{OP}(\text{OCH}_3)_3$ and the nitrile ylide which is capable of further reactions.¹⁹ Both attempts failed to give any product, and the starting materials were obtained in 80% to 95% yield. The reaction was repeated with the "activated" diethylbenzylcarbonyl phosphonate 23 in cyclohexane, and the adduct, diethyl-[(2,2-dimethyl-4,5-diphenyl-3-oxazolin-5-yl)-phosphonate] 24, was isolated in 42% yield. See Scheme 9.

Scheme 9



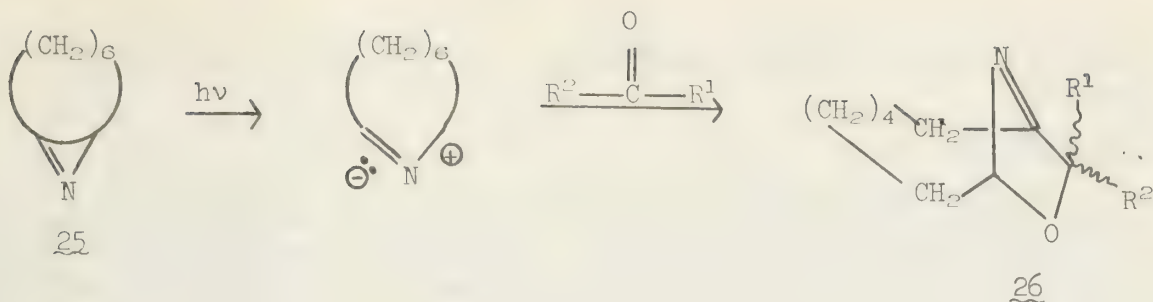
Products were also obtained where C2 was substituted with H, phenyl, and H, CH_3 , respectively. Several other 3-oxazolin-phosphonates were prepared, and the $\text{P}=\text{O}$ bond was seen not to react; showing that the $\text{P}=\text{O}$ bond of α -carbonyl phosphonates is not sufficiently activated so as to take part in the reaction. The bond still did not react upon using the substrate diethylvinyl phosphonate, which led to the formation of Δ^1 -pyrrolines. Irradiation of 2,2-dimethylazirine with diethylethoxycarbonyl phosphonate yielded diethyl-[(5-ethoxy-2,2-dimethyl-4-phenyl-3-oxazolinyl--phosphonate] in 96% yield. When the reaction was attempted with 2,3-diphenyl-2H-azirine, only the known azirine dimers 2-*exo*, 4,5,6-*exo*- and 2-*endo*, 4,5,6-*exo*-tetraphenyl-1,3-diazabicyclo[3.1.0] hex-3-ene as well as tetraphenylpyrazine and 2,4,5-triphenylimidazole were obtained. The same products were obtained when the azirine was added dropwise to the phosphonate. The only rationale offered was that the ylide produced simply reacted more rapidly with the azirine than with the phosphonate.

Cyanides

Phenylazirines have been found to react with the keto groups in acylcyanides affording 5-cyano-3-oxazolines.¹² These reactions proceeded with the same regiospecificity as did those with ketones. As expected, at no time was the CN group seen to react in the examples reported. This was not the case in the irradiation of 2,3-diphenyl-2H-azirine in the presence of 1-cyanoethyl formate. In this example, 2,4-diphenyl-5-ethoxy-5-cyano-3-oxazoline (*cis*--*trans* mixture) and 2,5-diphenyl-4-ethoxycarbonyl-imidazole were isolated in 30% and 14% yields, respectively.²⁰ Nitriles which are activated are much more likely to yield non-oxazoline products.

Bicyclic 3-Oxazolines

The purely aliphatic azirine 2,3-dipropyl-2H-azirine, reacted with substrates such as acetone or the activated methyl trifluoroacetate to form the corresponding 3-oxazolines in 14% and 65% yields, respectively, upon irradiation.¹⁵ The adduct of the activated substrate had a *cis*--*trans* ratio of 1:2.1 (not necessarily respectively). The success of this case of an aliphatic azirine led to the irradiation of 9-azabicyclo [6.1.0] non-1(9)-ene 25 in the presence of each of methyl trifluoroacetate, methyl difluoroacetate, 1,1,1-trifluoropropanone, and acetone. The resulting bicyclic 3-oxazolines 26 were obtained in yields of 60%, 27%, 61%, and 17%, respectively. As usual, cycloaddition was regiospecific but not stereospecific; hence the usual ylide intermediate was assumed as illustrated in Scheme 10.



Scheme 10

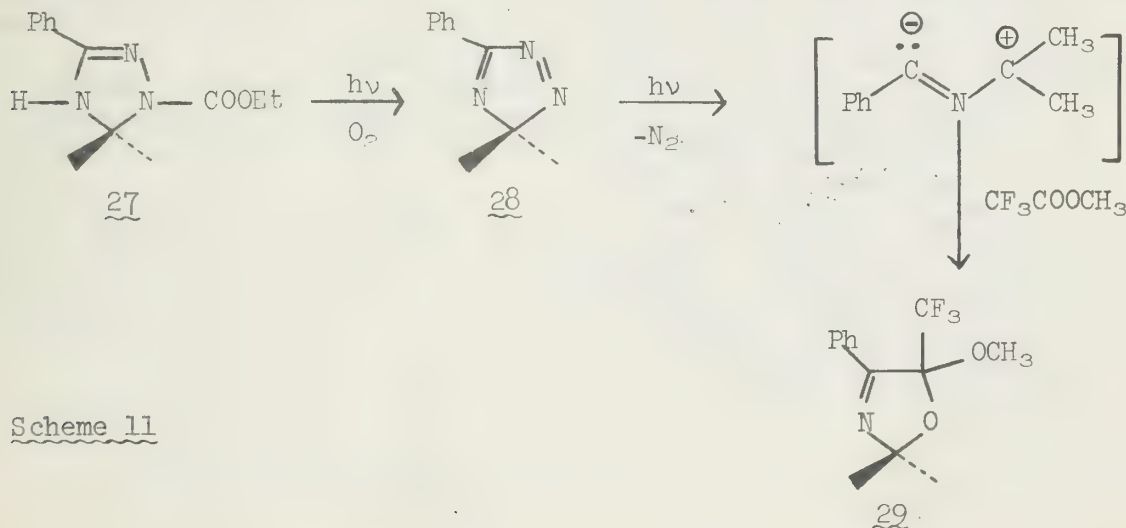
Table I

Compound	R ¹	R ²	Isomer Ratio	Percent Yield
26A	OCH ₃	CF ₃	2:1	60
26B	OCH ₃	CHF ₂	1.7:1	27
26C	CH ₃	CF ₃	1.1:1	61
26D	CH ₃	CH ₃	--	17

Irradiation took place from between 9 to 23 hours, and separation of the compounds was accomplished by gas chromatography. Absolute configuration could not be discerned for the first three cases, however, by observing the products A--D, one can speculate as to the origin of the ratios. For C, the ratio is 1.1:1, and it is known that the conformational energy of CH₃ and CF₃ is practically the same, though the electronic effects are quite different.¹⁵ In light of this information with that in Table I, one can deduce that the ratios of the stereoisomers are due to steric, and not electronic, effects. One can also reason that these steric effects favor the less bulky group on C10 being in the endo-position with respect to the methylenes as the central ring.

Triazolines

A photochemical approach to the synthesis of 3-oxazolines which does not use azirines, or have azirines as intermediates, is that of the irradiation of 1-carbethoxy-5,5-dimethyl-3-phenyl-Δ²-1,2,4-triazoline 27 in benzene in the presence of oxygen with an appropriate substrate as in Scheme 11. If the substrate was trifluoroacetic acid methylester, the adduct was 5-methoxy-2,2-dimethyl-4-phenyl-5-trifluoromethyl-3-oxazoline 29. This reaction was successfully carried out in 39% yield.²¹ The probable intermediate was 5,5-dimethyl-3-phenyl-1,2,4-triazole 28 which, upon losing nitrogen, gave the



Scheme 11

benzonitrile-isopropylide. The triazoline reaction did not work with ketones.

Applications

The applications of oxazolines in general, was well outlined in a review article by J. A. Frump in 1971.³ Even though, to this date, the 2-oxazolines have been the most useful, 3-oxazolines have shown much promise. Certain 3-oxazolines, which have long aliphatic side chains (e.g. $n\text{-C}_7\text{H}_{15}$) in the 2-position, have shown analgesic properties, stimulation and depression of the central nervous system, and strong sedative effects.²² 4-Amino-oxazolines were found to be somewhat effective as skeletal muscle relaxants.⁵ In addition to the promising medical properties, 3-oxazolines have shown other industrial uses, with much of the work coming from the du Pont laboratories. Certain haloalkyl-4-alkoxy-3-oxazolines have been found useful as solvents for highly fluorinated polymers which yield solutions for rendering paper and fabrics water repellent.²³ Other uses include the modification of film-forming properties of polymethacrylates (4-amino-3-oxazolines having halogenated hydrocarbon substituents in the 2- and 5-positions), flame proofing, heat-exchange fluids, and hydraulic fluids.²⁴ With respect to photochemistry, 3-oxazolines have been used in the study of the ring openings and regioselectivity in the photocycloadditions of substituted azirines and other compounds.

BIBLIOGRAPHY

1. H. O. L. Fischer, G. Dangschat, and H. Stettiner, Ber., 65 B, 1032 (1932).
2. R. H. Wiley and L. L. Bennett, Jr., Chem. Rev., 44, 447 (1949).
3. J. A. Frump, Chem. Rev. 71, 483 (1971).
4. S. S. Chang, C. Hirai, B. R. Reddy, K. O. Herz, A. Kato, and G. Sipma, Chem. and Ind., London, 1639 (1968).
5. W. J. Middleton, D. Metzgen, K. B. Cunningham, and C. G. Krespan, J. Heterocyclic Chem., 7, 1045 (1970).
6. H. Giezendanner, M. Märky, B. Jackson, H. -J. Hansen, and H. Schmid, Helv. Chim. Acta, 55, 745 (1972).
7. H. Giezendanner, H. J. Rosenkranz, H. -J. Hansen, and H. Schmid, Helv. Chim. Acta, 56, 2588 (1973).
8. A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., Pure & Appl. Chemistry, 33, 269 (1973). A. Padwa, S. Clough, M. Dharan, J. Smolanoff, S. I. Wetmore, Jr., J. Amer. Chem. Soc., 94, 1395 (1972).
9. W. Sieber, P. Gilgen, S. Chaloupka, H. -J. Hansen and H. Schmid, Helv. Chim. Acta, 56, 1679 (1973).
10. H. Giezendanner, H. Heimgartner, B. Jackson, T. Winkler, H. -J. Hansen, and H. Schmid, Helv. Chim. Acta, 56, 2611 (1973).
11. P. Claus, Th. Doppler, N. Gakis, M. Georgarakis, H. Giezendanner, P. Gilgen, H. Heimgartner, B. Jackson, M. Märky, N. S. Narasimhan, H. J. Rosenkranz, A. Wunderli, H. -J. Hansen, and H. Schmid, Pure & Appl. Chemistry, 33, 339 (1973).
12. P. Claus, P. Gilgen, H. -J. Hansen, H. Heimgartner, B. Jackson, and H. Schmid, Helv. Chim. Acta, 57, 2173 (1974).
13. U. Schmid, P. Gilgen, H. Heimgartner, H. -J. Hansen, and H. Schmid, Helv. Chim. Acta, 57, 1393 (1974).
14. H. Heimgartner, P. Gilgen, U. Schmid, H. -J. Hansen, and H. Schmid, Chimia, 26, 424 (1972).
15. A. Orahovats, H. Heimgartner, and H. Schmid, Helv. Chim. Acta, 57, 2626 (1974).
16. B. Jackson, N. Gakis, M. Märky, H. -J. Hansen, W. von Philipsborn, and H. Schmid, Helv. Chim. Acta, 55, 916 (1972).

17. N. Gakis, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, 58, 748 (1975).
18. K. Burger, J. Fehn, and E. Moll, *Ber.*, 104, 1826 (1971).
19. K. Burger, K. Einbellig, G. Süss, and A. Gieren, *Angew. Chem. Int. Ed. Engl.*, 12, 156 (1973).
20. B. Jackson, M. Märky, H. -J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 55, 919 (1972).
21. P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta*, 57, 1382 (1974).
22. E. Jassmann and H. Schulz, *Pharmazie*, 18, 461, 527 (1963).
23. W. J. Middleton, U. S. Patent, 3,461,129 (1969). *Chem. Abstr.*, 71, 101840v (1969).
24. W. J. Middleton, U. S. Patent, 3,310,570 (1967). *Chem. Abstr.*, 67, 21904w (1967).

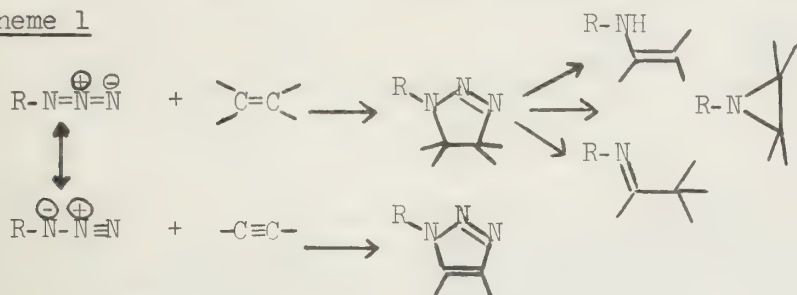
RECENT SYNTHETIC APPLICATIONS OF THE 1,3-DIPOLAR ADDITION OF AZIDES TO CARBON-CARBON MULTIPLE BONDS

Reported by Mark S. Pavlin

September 29, 1975

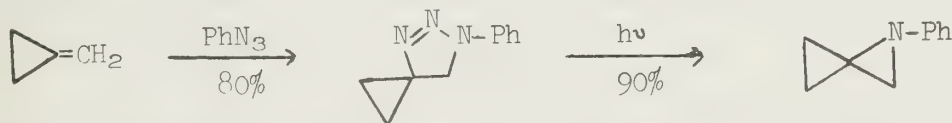
Under mild thermal conditions organic azides add in a concerted 1,3-fashion to various polarophiles including alkenes and alkynes which yield Δ^2 -1,2,3-triazolines and 1H-1,2,3-triazoles respectively (Scheme 1).¹ The alkene reaction may also lead to aziridines, enamines and imines via thermal or photolytic decomposition of the often unstable triazolines.

Scheme 1



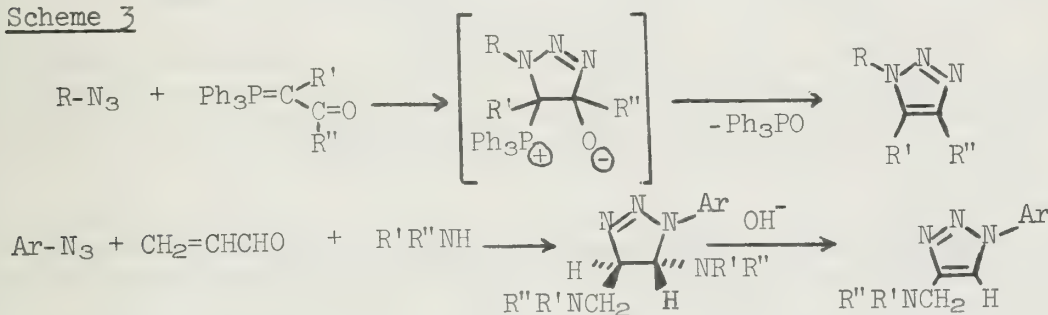
Recent work has greatly expanded the scope and synthetic usefulness of these reactions. For example, photolysis of the triazolines prepared from methylene and benzylidene cyclopropane and phenyl azide afforded the first known 1-azaspiro[2,2]pentanes (Scheme 2).² Triazoles have been synthesized

Scheme 2



by two novel routes (Scheme 3)^{3,4} as well as by the older method (Scheme 1) applied to new acetylene derivatives.⁵ Ynamines⁶ and alkoxy acetylenes⁷ react with sulfonyl azides but yield ring-opened guanyl diazomethanes rather than the expected triazoles. Other diazo compounds of interest result from azide addition to cyclopropenes⁸ and cinnamic acid derivatives.⁹

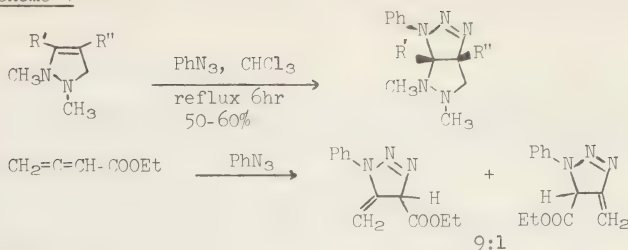
Scheme 3



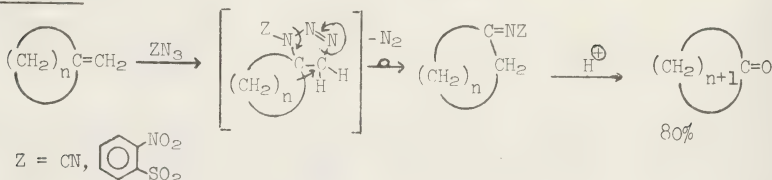
Addition is most rapid with electron-rich or electron-poor multiple bonds¹⁰ and is regioselective.⁵ Thus Δ^3 -pyrazolines gave pyrazolidino[4,3-d]-triazolines¹¹ and carbethoxyallene gave mainly 1-phenyl-4-carbethoxy-5-methylene-1,2,3-triazoline¹² when treated with phenyl azide (Scheme 4).

Perhaps the most valuable azide olefin reaction is the carbocyclic ring expansion sequence introduced by McMurry and Coppolino¹³ and modified by Wohl (Scheme 5).¹⁴ Interestingly, Wohl has also developed an analogous ring contraction sequence using cyclic vinyl ethers.¹⁵ Also, sulfonyl azides add to simple olefins, albeit slowly, giving imines or enamines which can be converted to ketones or sulfonamides.¹⁶

Scheme 4



Scheme 5



Finally, since the triazolines formed by aryl azide addition to many olefinic bonds are stable crystalline solids, azide additions to highly reactive¹⁷ or unstable¹⁸ compounds afford characterizable derivatives.

BIBLIOGRAPHY

1. Cycloaddition reactions have been reviewed by Huisgen, *Ang. Chem. Int. Ed. Eng.*, **2**, 565 and 633 (1963). Azide 1,3-dipolar additions have been reviewed by L'abbe, *Chem. Rev.*, **69**, 345 (1969).
2. D. A. Aug, R. B. Lorens, and G. S. Helwig, *Tetrahedron Lett.*, 4795 (1973); J. K. Crandall and W. W. Conover, *J. Org. Chem.*, **39**, 63 (1974).
3. G. L'abbe and H. J. Bestmann, *Tetrahedron Lett.*, 63 (1969); G. L'abbe, P. Ykman, and G. Smets, *Tetrahedron*, **25**, 5421 (1969); P. Ykman, G. L'abbe, and G. Smets, *Tetrahedron*, **29**, 195 (1973).
4. D. Pocar, R. Stradi, and L. M. Rossi, *J. Chem. Soc., Perkin Trans. I*, 619 and 769 (1972).
5. G. L'abbe, J. E. Galle, and A. Hassner, *Tetrahedron Lett.*, 303 (1970); A. N. Pudovik, N. G. Khusainova, and Z. A. Nasybullina, *Zh. Obshch. Khim.*, **43**, 1683 (1973).
6. G. Himbert and M. Regitz, *Synthesis*, 571 (1972).
7. G. Himbert and M. Regitz, *Chem. Ber.*, **105**, 2975 (1972).
8. M. Franck-Neumann and C. Buchecker, *Tetrahedron Lett.*, 2659 (1969); D. H. Aue and G. S. Helwig, *Tetrahedron Lett.*, 721 (1974).
9. F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 3642 (1971).
10. R. Sustmann and H. Trill, *Ang. Chem. Int. Ed. Eng.*, **11**, 838 (1972).
11. R. Jacquier, C. Pellier, C. Petrus, and F. Petrus, *Bull. Soc. Chim. Fr.*, 4078 (1971).
12. P. Battioni, L. Vo-Quang, and Y. Vo-Quang, *Cr. Rev. Acad. Sci., C*, **275**, 1109 (1972).
13. J. E. McMurry, *J. Amer. Chem. Soc.*, **91**, 3676 (1969); J. E. McMurry and A. P. Coppolino, *J. Org. Chem.*, **38**, 2821 (1973).
14. R. A. Wohl, *J. Org. Chem.*, **38**, 3862 (1973).
15. R. A. Wohl, *Tetrahedron Lett.*, 3111 (1973).
16. R. A. Abramovitch, G. N. Knaus, M. S. Pavlin, and W. D. Holcomb, *J. Chem. Soc., Perkin Trans. I*, 2169 (1974).
17. A. Krebs and D. Byrd, *Justus Liebigs Ann. Chem.*, **707**, 66 (1967).
18. A. J. Birch and P. G. Lehman, *Tetrahedron Lett.*, 2395 (1974).

BIFUNCTIONAL CATALYSIS

Reported by Terry Lewis

October 6, 1975

Bifunctional catalysis may be most broadly defined as the action of two catalytic entities, linked in some manner, on a second substrate molecule which is undergoing reaction. The possibility of such a catalyst was first envisioned in a qualitative manner by Lowry¹ in the mid-1920's, but was not realized experimentally until the early 1950's through the pioneering work of Swain.² Only recently have significant advances been made in aqueous systems, primarily by Hine and co-workers, and these will comprise the bulk of this seminar.

One obvious reason to study multi-functional catalysis in relatively simple systems is to gain insight into the mechanism of enzyme action, which has been fairly conclusively shown in several systems to involve general acid and base catalysis.^{3,4} It is beyond the scope of this seminar to present examples of enzyme action where bifunctional catalysis has either been shown or is expected to be present; reference to biological systems will be given only when comparison seems especially pertinent. Bifunctional catalysis has been investigated in both aqueous and non-aqueous systems, and in thermal reactions in the solid state.

General Acid and Base Catalysis

Since most catalysts which act bifunctionally may be included within the category of general acid- or base-catalysts, a brief review of the subject will be included here.⁵ Brønsted and co-workers demonstrated that it was possible to divide reactions catalyzed by acids or bases into two categories: 1) specific acid or base catalysis in which the catalysis is kinetically attributable only to the conjugate acid or base of the solvent; and 2) general acid or base catalysis in which catalysis is kinetically attributable to all the acids and/or bases in solution.

An example which demonstrates this distinction is the general acid catalysis in the hydrolysis of ethyl orthoacetate.⁶ When this reaction



was studied under conditions in which the further hydrolysis of product was negligible and the concentration of the acids and bases present remained essentially constant, the reaction was found to be first order in ethyl orthoacetate. The rate constant for specific acid catalysis was measured as a function of hydronium ion concentration, and specific base catalysis was shown to be negligible. When the reaction was carried out in *m*-nitrophenol-sodium *m*-nitrophenolate buffers of various concentrations, the reaction rate increased with increasing *m*-nitrophenol concentration, even though the H_3O^+ concentration remained constant. Thus, some of the catalysis is due to undissociated *m*-nitrophenol, and the observed rate constant must be expressed as the sum of the terms for all the acids present. The term involving k_w

$$k = k_w [\text{H}_2\text{O}] + k_n [\text{H}_3\text{O}^+] + k_n [\textit{m}\text{-nitrophenol}]$$

is included for the "uncatalyzed" reaction with the acid water. For reactions which are catalyzed by general acids, the rate constant must

be expressed as the sum of the concentration of every acid present multiplied by its catalytic constant. The same type of relationship holds true for general base catalysis.

Certain reactions are subject to both general acid and general base catalysis, and rate expressions of

$$k = \sum_i k_i [\text{acid}_i]$$

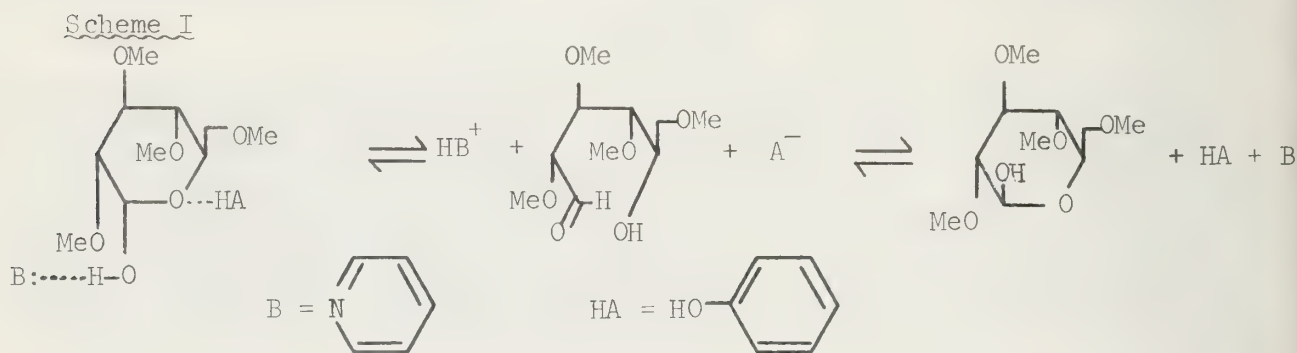
$$k = \sum_i k_i [\text{base}_i]$$

the form $k = \sum_i k_i [\text{base}_i] + \sum_j k_j [\text{acid}_j]$ and $k = (\sum_i k_i [\text{base}_i]) (\sum_j k_j [\text{acid}_j])$

have been suggested in these cases. The former expression seems to be of greater general importance and applicability in aqueous solution,^{7,8} although rate terms compatible with the latter expression have been found in several cases.^{9,10}

Mutarotation of Tetramethylglucose

The classic example of bifunctional catalysis is the 2-pyridone-catalyzed mutarotation of tetramethylglucose (TMG). Swain and Brown found² that in benzene, mixtures of phenol and pyridine act as efficient catalysts in the mutarotation of TMG; however, phenol or pyridine alone in benzene showed almost no catalytic activity. The reaction displayed third order kinetics overall, first order in each of pyridine, phenol and TMG. Swain and Brown rationalized these results in terms of Scheme I. The observed

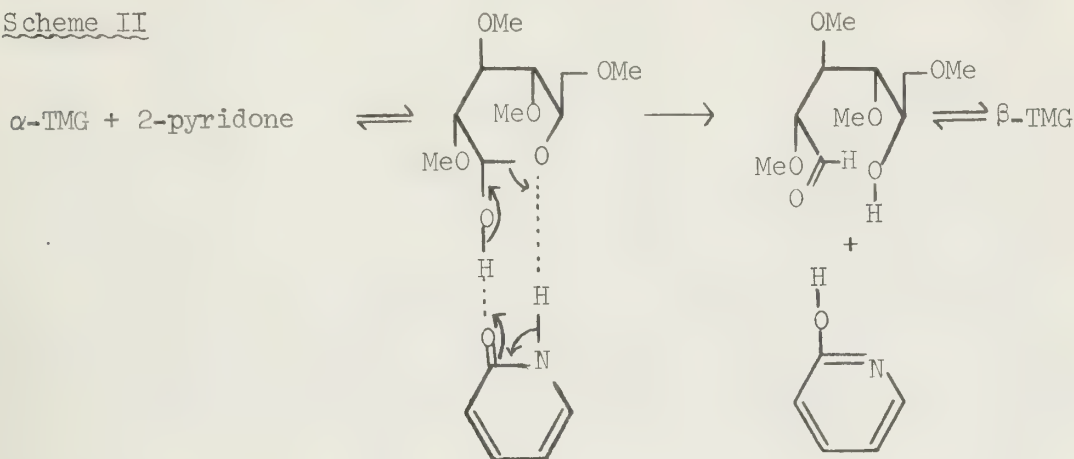


third order kinetics were explained by a concerted attack of both the acid and the base upon the substrate such that neither the conjugate acid nor the conjugate base of the sugar is an intermediate. It should be noted that this termolecular mechanism is not the only possibility which fits the kinetic data. If the phenol-pyridine ion-pair (which is known to exist in benzene solution¹¹) was acting as a general base catalyst, the same overall third order kinetics would result.^{12,13} The kinetic plausibility of the ion-pair general base-catalyzed reaction is not conclusive evidence against the termolecular mechanism. The situation is further confused by the greatly enhanced rates observed when ions are added to reactions involving polar intermediates in non-polar solvents.^{14,15}

Regardless of the true mechanism of TMG mutarotation in benzene by phenol-pyridine, Swain proposed on the basis of his observations that if the acid and base were properly oriented in one molecule, bifunctional catalysis should result. When 2-pyridone was used as the catalyst, greatly enhanced rates of mutarotation were observed; even though 2-pyridone is 1% as strong an acid as phenol and 0.01% as strong a base as pyridine. At high dilution (0.001 M catalyst) rates were observed to be 7000 times those calculated for phenol-pyridine catalysis at the same concentrations. This rate acceleration was explained in terms of Scheme

II. Inspection of molecular models indicates that the geometry is suitable for complex formation, and enhanced optical rotations of TMG were observed which are also indicative of a chelated type complex.

Scheme II

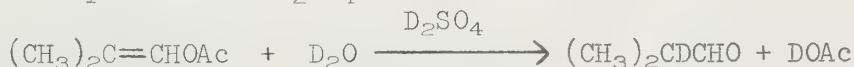


The optimal geometry of the complex and the avoidance of any highly charged intermediate in the non-polar solvent have been proposed to be of greater importance than the actual acid-base properties of the catalyst.¹⁶ Benzoic acid has catalytic efficiency and activation parameters¹⁶ parallel to those of 2-pyridone, even though it is a weaker base and a stronger acid. Since in both of these cases (as well as in the cases of similar catalysts) tautomeric forms of the catalyst are involved in the mechanism, this phenomenon may more appropriately be termed tautomeric catalysis¹⁶ rather than acid-base bifunctional catalysis.¹⁷

Dedeuteration of Isobutyraldehyde-2-d

When designing a catalyst which is to be tested for bifunctionality, a fundamental knowledge of the monofunctional entities to be included is necessary. Although the removal of α -hydrogen from carbonyl compounds has been the subject of considerable research, the use of aldehydes as substrates and amines as catalysts had received relatively little attention, probably because of their frequent incompatibility with the halogens often used in the rate studies. Hine and co-workers therefore, undertook a systematic investigation of the dedeuteriation of isobutyraldehyde-2-d by various amines.

The aldehyde was prepared by the reaction of D_2O with isobutenyl acetate in the presence of D_2SO_4 . Kinetic studies were carried out in



aqueous solutions under pseudo-first order conditions, amine concentration remained constant. The removal of deuterium was followed by an nmr method which was based on a graph constructed with data on known mixtures of protium and deuterium aldehyde in aqueous solution.¹⁸ Since the deuterium exchange is catalyzed by strong acid and by strong and weak bases, the rate constants were corrected to be indicative of only the amine-catalyzed portion of the reaction. Catalysis of α -deuterium exchange by relatively unhindered tertiary amines fit the Brønsted catalysis equation satisfactorily, but sterically hindered amines such as 2,6-

lutidine were seen to be less than 1% as reactive as expected from their basicities. The most reactive amines for their basicities were the unhindered saturated amines, 1,4-diazabicyclo[2.2.2]octane (DABCO) and trimethylamine.¹⁸ In the cases of secondary amines, no significant amount of catalysis of deuterium exchange via resultant iminium ion formation was observed.¹⁹ In the presence of excess methylamine, most of the aldehyde is present in the form of its N-methylimine, and most of the exchange took place via attack of methylamine on the corresponding iminium ion with a rate proportional to the product $[\text{Me}_2\text{CDCH}=\text{NHMe}^+][\text{MeNH}_2]$.^{20,21} When the R group of the primary amine was larger than methyl, significant equilibrium amounts of imine are also formed.²² The resulting iminium ions are of the E configuration, as determined by nmr²² and by analogy to 4-methyl-2-pentene, in which the E isomer is 1.2 kcal/mole more stable than the Z isomer.²³ Thus, it seemed plausible that a bifunctional catalyst could be found, in which both a primary amine group (for imine formation) and another basic group (for deuterium removal from the iminium ion) were located on the same molecule, allowing intramolecular deuterium removal.

Although catalysts of the type $\text{H}_3\text{N}(\text{CH}_2)_n\text{CO}_2^-$ and $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2$ where n was 1-5 and 2-5, respectively, gave no evidence of bifunctional activity in the dedeuteration of isobutyraldehyde-2-d,^{24,25} both 1-dimethylamino-8-amino-2-octyne²⁵ and various polyethylenimines (PEI's)^{26,27} were shown to have bifunctional activity. PEI's are sometimes represented by the simplified formula $(\text{CH}_2\text{CH}_2\text{NH})_n$, although they have a degree of branching such that the ratio of 1°2°3° amine groups is about 1:2:1. PEI-X represents a polymer of average molecular weight X, and PEI normalities refer to the number of equivalents of amine groups per liter of solution.

With a given initial concentration of isobutyraldehyde-2-d, the pseudo first order rate constants increased with increasing PEI concentration at low PEI concentrations but levelled off at high PEI concentrations.²⁷ An obvious interpretation of these results is that the dedeuteration is occurring almost entirely via a complex formed between aldehyde and PEI. Also indicative of complex formation are uv measurements at 285 nm (λ_{max} of the aldehyde). Using PEI solutions without the aldehyde as reference, it was observed that the decrease in absorbance closely reflected the increase in dedeuteration.²⁷ Although such a decrease in absorbance could indicate the formation of an adduct other than an imine,²⁸ absorption spectra of the aldehyde in the presence of excess PEI showed a maximum around 244 nm, which is plausible for an isobutyraldimine derivative but not for a simple imidazolidine. Since PEI's may be considered to be collections of primary, secondary and tertiary amine groups bridged by ethylene segments, it is worthwhile to compare the catalytic activities of PEI and ethylenediamine and its N-methyl and N-ethyl derivatives (Table 1).

Table 1.²⁷ First-order rate constants for the dedeuteration of 0.053 M isobutyraldehyde-2-d at 35° and pH 8.51 ± 0.04

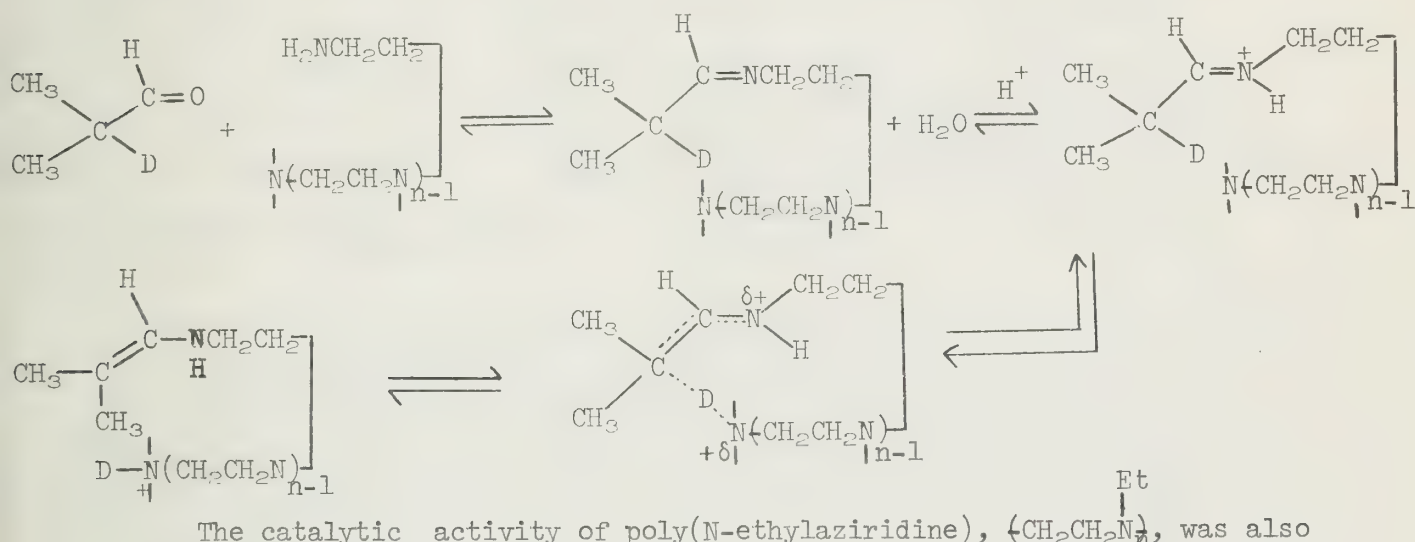
Catalyst ^a	10 ⁶ k _p sec ⁻¹	Catalyst ^a	10 ⁶ k _p sec ⁻¹
H ₂ NCH ₂ CH ₂ NH ₂	2.0	EtNHCH ₂ CH ₂ NH ₂	4.6
MeNHCH ₂ CH ₂ NH ₂ ^b	3.0	Et ₂ NCH ₂ CH ₂ NH ₂	3.7
MeNHCH ₂ CH ₂ NHMe	3.6	Et ₂ NCH ₂ CH ₂ NH ₂	5.5
Me ₂ NCH ₂ CH ₂ NH ₂	15	Et ₂ NCH ₂ CH ₂ NEt ₂	3.3
Me ₂ NCH ₂ CH ₂ NHMe	23	PEI-600 ^c	75
Me ₂ NCH ₂ CH ₂ NMe ₂	35	PEI-1200 ^d	79
EtNHCH ₂ CH ₂ NH ₂	3.4	PEI-1800 ^e	70

^a0.100 ± 0.001 N unless otherwise noted. ^b0.097 N. ^c0.103 N.

^d0.113 N. ^e0.104 N.

If the ethylenediamine and its N-ethylated derivatives are taken as the best models, the PEI's may be seen to be 12-36 times as effective as catalysts as they would be expected to be if they were acting monofunctionally. If the PEI's were acting simply as basic catalysts, their efficiency would be expected to decrease with decreasing pH; instead the catalytic efficiency of 0.97 N PEI-1800 is at a maximum near pH 8.0. This behavior is that predicted by Hine's proposed mechanism; above pH 8 the reaction rate is slower because a smaller fraction of the imine formed is protonated to give iminium ion, and below pH 8 the rate is slowed by the decreased number and basicity of free amine groups available for internal dedeuteration. If the iminium ion derived from the PEI-1800 and the aldehyde was dedeuterated by a PEI molecule other than the one to which it was complexed, the reaction rate would be expected to increase with increasing PEI concentrations above those at which most of the aldehyde had been complexed; no such trend is observed. Dedeuteration by water and by hydroxide ion under the conditions used were also shown to be negligible. Thus, it seems that near the pH of maximum effectiveness, catalysis by PEI-1800 appears to consist largely of rate-limiting attack by internal amine groups on isobutyraldehyde-2-d complexed to the PEI in the form of iminium ions (Scheme III).

Scheme III.

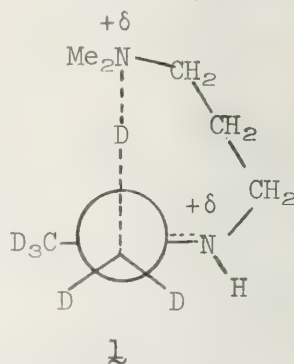


The catalytic activity of poly(N-ethylaziridine), $(\text{CH}_2\text{CH}_2\text{N})_n$, was also measured²⁷ in order to test the possibility that all polymeric amines are particularly good catalysts in the dedeuteration reaction. The catalytic efficiency of this polymer at pH 8.47 was less than 1/10 that of PEI solutions which were only half as concentrated. Since catalysis via a push-pull mechanism could also occur with poly(N-ethylaziridine), the validity of Scheme III is reinforced.

Since the iminium ion formed in Scheme III is of the E configuration, a rather large cyclic transition state is required. The observed bifunctional catalysis by 1-dimethylamino-8-amino-2-octyne²⁵ should involve a 13-membered ring transition state. With a computer-simulated polymerization of ethylenimine used to estimate the detailed structure of the PEI's in addition to data on various reference reactions, Hine has argued that the complexed aldehyde is probably dedeuterated most efficiently by amino groups that are 3-6 monomer units from the complexed aldehyde.²⁹ This would correspond to a 13-22-membered cyclic transition state.

Dedeuteration of Acetone-d-6

By means of a thorough preliminary investigation of the kinetics of monofunctional catalysis of deuterium removal from acetone-d-6 by amines,³⁰ and of the kinetics of the formation of imines by various primary amines,³¹ Hine has proposed that bifunctional catalysis is the major pathway for dedeuteration of acetone-d-6 in certain cases. Catalysis constants of the monoprotonated forms of 3-dimethylaminopropylamine and *cis*- and *trans*-2-(dimethylaminomethyl)cyclopentylamines (DAMCA's) are much larger than expected by simple basic catalysis.³³ The activity of the *cis*- and *trans*-DAMCA's are 35-150 and 17-75, respectively, times the values expected for monofunctional catalysis. The experimental data are most consistent with a mechanism involving intramolecular deuterium removal by the dimethylamino group of the iminium ion formed by the catalyst and acetone-d-6. Such a mechanism requires a cyclic transition state as shown in 1. Molecular models indicate that a transition state such as 1 is compatible with the proposed bifunctional catalysts. The eclipsing of carbons 1 and 2 of 3-dimethylaminopropylamine necessary to reach the conformation in 1 may explain in part why the DAMCA's are such effective catalysts; in these cases the eclipsing of the analogous carbon atoms is included in the ground state of the molecule. Similar stereoelectronic factors are observed in the internal hydrogen shift in the radical cation derived from an alkyl vinyl ether. The principal internal hydrogen shift in the radical cation of n-heptyl vinyl ether proceeds by a transition state containing an 8-membered ring similar to the ring shown in 1.³⁴

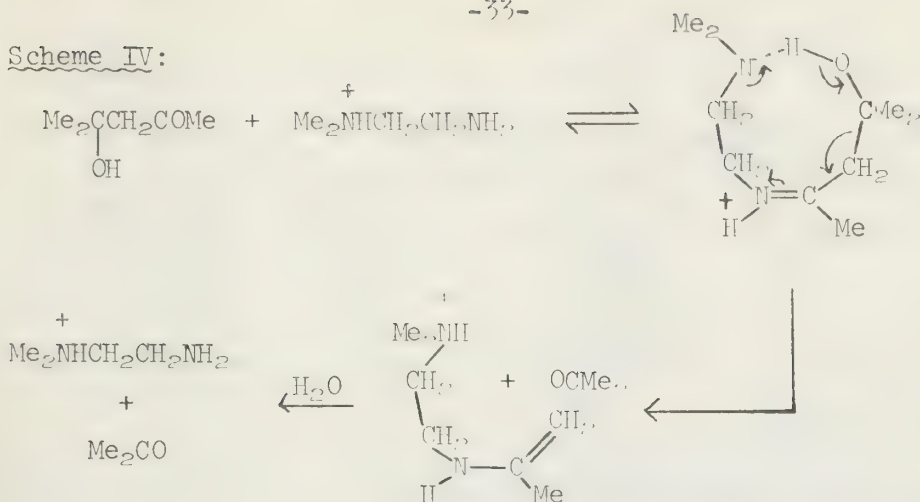


Westheimer has shown that the decarboxylation of acetoacetic acid by the decarboxylase from *Clostridium acetobutylicum* involves the intermediate formation of an enamine of acetone, which is then hydrolyzed to acetone.³⁵ The observed catalytic efficiency of the enzyme in the deuterium exchange of acetone-d-6³⁶ is good evidence that the hydrolysis is assisted by internal catalysis by the enzyme. On a weight basis the efficiency of the DAMCA's compare favorably to the catalytic activity of the enzyme in the dedeuteration of acetone-d-6.³³

Dealdolization of Diacetone Alcohol

The dealdolization of diacetone alcohol ($\text{Me}_2\text{COHCH}_2\text{COMe} \rightarrow 2\text{Me}_2\text{CO}$) is known to be catalyzed by primary and secondary amines and by hydroxide ion.³⁷ Hine has found³⁷ that the catalytic activity of the monoprotonated form of dimethylaminoethylamine (38% protonation at the tertiary nitrogen³⁸) is somewhat larger, about four times, than is expected by a comparison of activities of other neutral and protonated diamines. Imine formation has been shown to be significantly faster than dealdolization in the cases of primary amines of varying basicity, indicating carbon-carbon bond cleavage to be rate controlling.³⁷ Therefore, the ability of the protonated dimethylamino group to act as an internal acid-catalyst in imine formation should not significantly increase the rate of dealdolization. The protonated diamine may be acting bifunctionally as shown in Scheme IV. The catalyst and diacetone alcohol react to give an intermediate iminium ion in which the alcoholic proton is hydrogen bonded to the dimethylamino group of the catalyst. Proton removal by the tertiary amine followed by hydrolysis of the resulting enamine yields

Scheme IV:



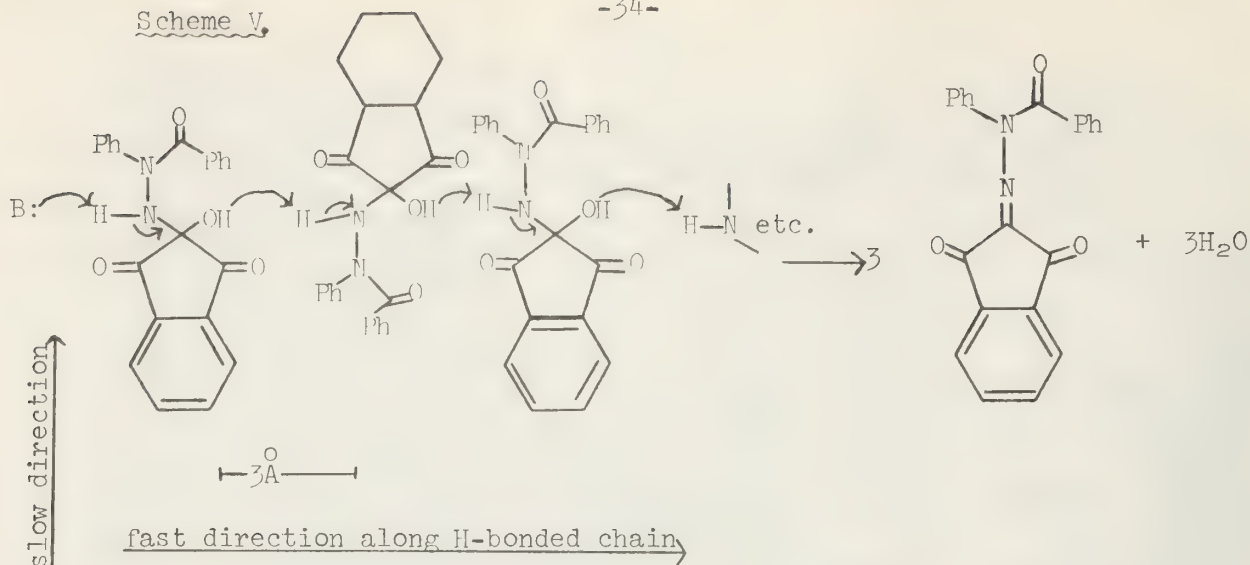
acetone and regenerated catalyst. This mechanism requires a 9-membered cyclic transition state which may be unnecessarily large, since molecular models indicate that a ring as small as 7-membered would meet the stereoelectronic requirements of a preferred linear hydrogen bond and coplanarity of the intermediate iminium ion.

It should be noted that dealdolization of hexose derivatives by Class I aldolases is thought to involve iminium ion formation between carbonyl and a lysine residue, followed by base promoted cleavage, possibly by an imidazole ring of histidine or by carboxylate.^{39,3}

Solid State Catalysis

In general, the range of catalysts available in thermal solid state reactions is somewhat limited. The catalyst must be incorporated into the regular crystal lattice of the molecule, and in some cases the catalytic entities may actually be part of the substrate undergoing reaction. Swain recently observed⁴⁰ that, upon heating, the 1:1 complex of pyridinium chloride and triphenylmethanol yielded triphenylmethylchloride, water, and pyridine. One can envision pyridinium ion-assisted dehydration, followed by chloride capture of the partially formed carbonium ion. Although this reaction was carried out in the melt, it suggests that similar reactions could take place within the crystal lattice of single crystals, if the initial geometry was correct. Recently, single crystals of the carbinol hydrazine formed by the reaction of ninhydrin and α -benzoyl- α -phenylhydrazine were isolated and the dehydration to the corresponding benzoylphenylhydrazone was studied in the solid state.⁴¹ The dehydration reaction appeared to be anisotropic, and correlation of this anisotropy with the crystal structure of the initial carbinol hydrazine yielded the mechanism shown in Scheme V.

It can be seen that once the reaction has been initiated, the basic hydroxyl group and the acidic amine proton have almost the perfect geometry for catalysis to take place within the crystal lattice. The observed anisotropy of the reaction is convincing evidence for the importance of this catalytic effect, since the reaction proceeds more rapidly in the direction of the hydrogen bonded chains.



Summary

Bifunctional catalysis can be studied under a variety of experimental conditions. Although salt effects and molecular aggregation make interpretation of results more difficult in non-polar solvents, tautomeric catalysis has been observed in some cases. The observed bifunctionality of certain catalysts in dedeuteration and dealdolization reactions may serve as good models for related biological systems. Catalysis in the solid state offers a new approach to studying catalytic effects.

BIBLIOGRAPHY

1. T. M. Lowry, J. Chem. Soc., 2554 (1927).
2. C. G. Swain and J. F. Brown, Jr., J. Amer. Chem. Soc., 74, 2534, 2538 (1952).
3. W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, Inc., 1969.
4. M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", John Wiley and Sons, Inc., 1971.
5. For a more detailed discussion, see R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, N. Y., 1971.
6. J. N. Brønsted and W. F. K. Wynne-Jones, Trans. Faraday Soc., 25 59 (1929).
7. W. P. Jencks, Chem. Reviews, 72, 705 (1972).
8. W. P. Jencks, J. Amer. Chem. Soc., 94, 4731 (1972).
9. H. M. Dawson and E. Spivey, J. Chem. Soc. 2180 (1930).
10. C. G. Swain, J. Amer. Chem. Soc., 72, 4578 (1950).
11. C. G. Swain and J. F. Brown, Jr., J. Amer. Chem. Soc., 74, 2691 (1952).
12. Y. Pocker, Chem. Ind. (London), 968 (1960).
13. P. R. Rony, W. E. McCormack, and S. W. Wunderly, J. Amer. Chem. Soc., 91, 4244 (1969).
14. S. Winstein, S. Smith, and D. Darwish, J. Amer. Chem. Soc., 81, 5511 (1959).
15. A. M. Eastham, E. L. Blackall, and G. A. Latremouille, J. Amer. Chem. Soc., 77, 2182 (1955).
16. P. R. Rony, J. Amer. Chem. Soc., 90, 2824 (1968).
17. For other reported examples of this catalytic effect, see P. R. Rony, J. Amer. Chem. Soc., 91, 6090 (1969), and references cited therein.
18. J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, J. Amer. Chem. Soc., 87, 5050 (1965).
19. J. Hine and J. Mulders, J. Org. Chem. 32, 2200 (1967).

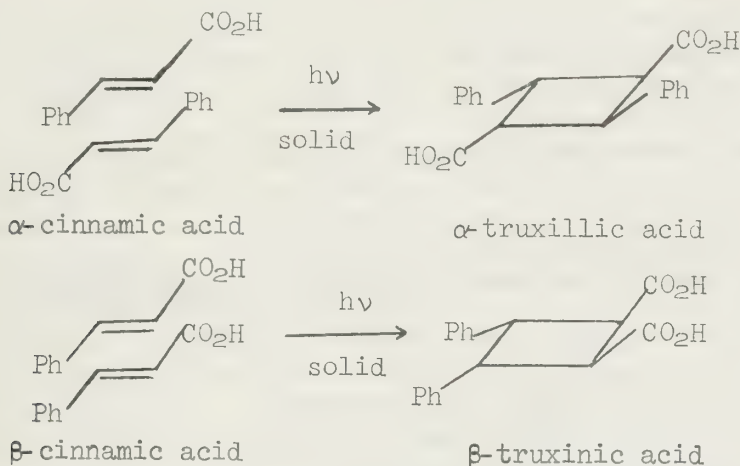
20. J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, J. Amer. Chem. Soc., 88, 3367 (1966).
21. J. Hine, J. Mulders, J. G. Houston, and J. P. Idoux, J. Org. Chem., 32, 2205 (1967).
22. J. Hine and C. Y. Yeh, J. Amer. Chem. Soc., 89, 2669 (1967).
23. A. Schriesheim and C. A. Rowe, Jr., J. Amer. Chem. Soc., 84, 3160 (1962).
24. J. Hine, B. C. Menon, J. Mulders, and R. L. Flachskam, Jr., J. Org. Chem., 34, 4038 (1969).
25. J. Hine, J. L. Lynn, Jr., J. H. Jensen, and F. C. Schmalstieg, J. Amer. Chem. Soc., 95, 1577 (1973).
26. J. Hine, F. E. Rogers, and R. E. Notari, J. Amer. Chem. Soc., 90, 3279 (1968).
27. J. Hine, E. F. Glod, R. E. Notari, F. E. Rogers, and F. C. Schmalstieg, J. Amer. Chem. Soc., 95, 2537 (1973).
28. J. Hine and K. W. Narducy, J. Amer. Chem. Soc., 95, 3362 (1973).
29. J. Hine and R. L. Flachskam, Jr., J. Org. Chem., 39, 863 (1974).
30. J. Hine, J. C. Kaufmann, and M. S. Cholod, J. Amer. Chem. Soc., 94, 4590 (1972).
31. J. Hine, M. S. Cholod, and W. K. Chess, Jr., J. Amer. Chem. Soc., 95, 4270 (1973).
32. J. Hine and W.-S. Li, J. Org. Chem., 40, 2622 (1975).
33. J. Hine, M. S. Cholod, and J. H. Jensen, J. Amer. Chem. Soc., 93, 2321 (1971), and J. Hine M. S. Cholod, and R. A. King, J. Amer. Chem. Soc., 96, 835 (1974).
34. M. Katoh and C. Djerassi, Chem. Commun., 1385 (1969); J. Amer. Chem. Soc., 92, 731 (1970).
35. F. H. Westheimer, Proc. Chem. Soc., London, 253 (1963).
36. W. Tagaki and F. H. Westheimer, Biochemistry, 7, 901 (1968).
37. J. Hine and W. H. Sachs, J. Org. Chem., 39, 1937 (1974), and references cited therein.
38. J. Hine, F. A. Via, and F. H. Jensen, J. Org. Chem., 36, 2926 (1971).
39. B. L. Horecker, O. Tsolas, and C. Y. Lai in "The Enzymes," Vol. 7, 3rd ed., P. D. Boyer, Ed., Academic Press, New York, N. Y., 1973, Chapter 6.
40. C. G. Swain and Y. Okamoto, J. Amer. Chem. Soc., 92, 3409 (1970).
41. S. A. Puckett, I. C. Paul, and D. Y. Curtin, submitted for publication.

ORGANIC SOLID STATE PHOTODIMERIZATION

Reported by Maurice J. Baillargeon

October 9, 1975

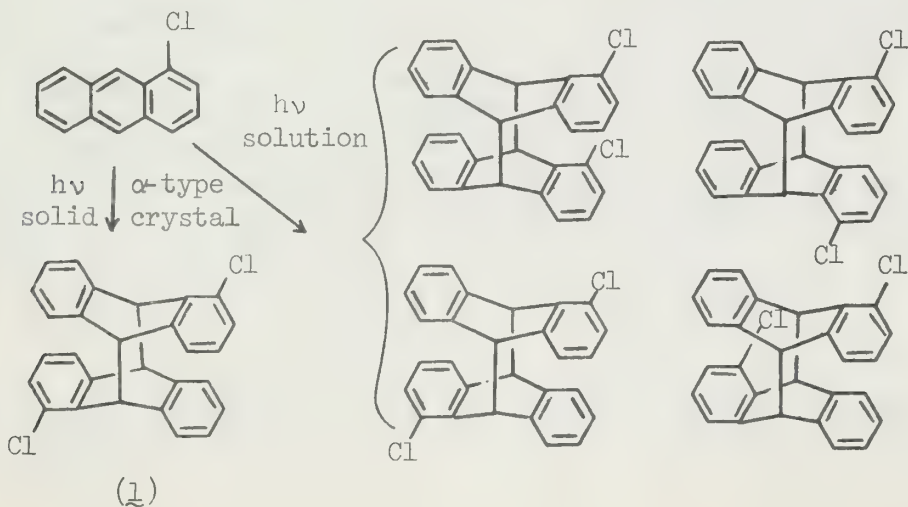
In the early 1920's deJong¹ obtained β -truxinic acid on uv irradiation of freshly precipitated trans-cinnamic acid.



On the other hand, he found that the longer the cinnamic acid stood before irradiation, the more of a second dicarboxycyclobutane, α -truxillic acid, was obtained. DeJong made use of two different crystalline ("polymorphic") forms of trans-cinnamic acid to account for his results.

Later work² verified deJong's work and it was in 1964 that Cohen and Schmidt^{3,4} using x-ray analysis showed that the nature of the product reflected the relative orientation of the phenyl rings in the solid cinnamic acids. From the cinnamic acid results a theory of topochemical control was advanced which stated that reactions in crystals proceeded with a minimum of atomic and molecular movement and were thus determined by the structure of the starting material.⁵

The photodimerization of anthracene and its derivatives has proved to be a suitable test of the topochemical preformation theory.⁶⁻¹⁰ For example, solid 1-chloroanthracene (α -form) yielded upon irradiation in the solid state exclusively one photodimer (1) while solution photolysis gave four photoproducts, of which the solid state photoproduct (1) comprised only 40% of the total mixture.⁶ Problems have been encountered, however,



in the photodimerization of 9-substituted anthracenes. For example, 9-cyanoanthracene yielded centric (head-to-tail or trans) dimers although packing in the crystal indicated that mirror-symmetric (head-to-head or cis) dimers were expected.^{6, 7}

Thomas has proposed that dislocations play a fundamental role in the production of the "abnormal" dimers.^{11, 12} There still exists, however, a variance of opinion as to the exact function of the dislocations or crystal defects in influencing the chemical behavior of a solid.^{5b, 13, 14}

Such solid state photochemistry has found other interesting applications. For example, asymmetric induction has been found in synthesis employing chiral crystals.¹⁵⁻¹⁶ Investigations of the uv-catalyzed photodimerization of pyrimidine bases have biochemical significance since such studies may bear on the problem of radiation damage to nucleic acids.¹⁷

BIBLIOGRAPHY

1. A. W. K. deJong, Ber., 55, 463 (1922).
2. H. I. Bernstein and W. C. Quimby, J. Amer. Chem. Soc., 65, 1845 (1943).
3. M. D. Cohen and G. M. J. Schmidt, J. Chem. Soc., 1996 (1964).
4. M. D. Cohen, G. M. J. Schmidt, and F. I. Sonntag, J. Chem. Soc., 2000 (1964).
5. For recent work see (a) G. M. J. Schmidt, Pure Appl. Chem., 27, 647 (1971); (b) M. D. Cohen, Angew. Chem., Int. Ed. Engl., 14, 386 (1975).
6. J. C. J. Bart and G. M. J. Schmidt, Israel J. Chem., 9, 429 (1971).
7. E. Heller and G. M. J. Schmidt, Israel J. Chem., 9, 449 (1971).
8. J. P. Desvergne, J. M. Thomas, J. O. Williams, and H. Bouas-Laurent, J. C. S. Perkin II, 363 (1974).
9. J. M. Thomas, J. O. Williams, J. P. Desvergne, G. Guarini, and H. Bouas-Laurent, J. C. S. Perkin II, 84 (1975).
10. M. M. Julian, Acta Cryst. A, 29, 116 (1973).
11. J. M. Thomas and J. O. Williams, Progr. Solid-State Chem., 6, 121 (1971).
12. J. O. Williams and J. M. Thomas, Trans. Faraday Soc., 63, 1720 (1967).
13. M. D. Cohen, Z. Ludmer, J. M. Thomas, and J. O. Williams, Proc. R. Soc. Lond. A., 324, 459 (1971).
14. A. Kawada and M. M. Labes, Mol. Cryst. and Liq. Cryst. 11, 133 (1970).
15. B. S. Green, M. Lahav, G. M. J. Schmidt, Mol. Cryst. Liq. Cryst., 29, 187 (1975).
16. A. Elgavi, B. S. Green, G. M. J. Schmidt, J. Amer. Chem. Soc., 95, 2058 (1973).
17. (a) H. Ishihara, Photochim. and Photobiol. 2, 455 (1963);
(b) R. F. Stewart, Biochim. Biophys. Acta, 75, 129 (1963);
(c) E. Fahr, Angew. Chem., Int. Ed. Engl., 8, 578 (1969),
(d) N. J. Leonard, R. S. McCredie, M. W. Logue, and R. L. Cundall, J. Amer. Chem. Soc., 95, 2320 (1973);
(e) J. K. Frank and I. C. Paul, J. Amer. Chem. Soc., 95, 2324 (1973).

COAL METHANATION

Reported by Robert Mason

October 16, 1975

Introduction

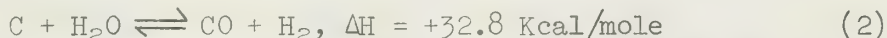
Coal, a carbonaceous material of varying composition, constitutes nearly 80% of the U. S. fuel reserves.¹⁻³ In contrast, natural gas is expected to be in short supply in the near future. Due to the economic advantages of natural gas, processes for converting coal to substitute natural gas (SNG) have been developed and are becoming commercially feasible.⁴

Structure of Coal

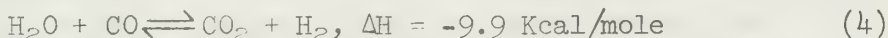
Based on permanganate⁵ and oxygen⁶ oxidation, and decarboxylation studies⁷ of devolatilized bituminous coals, the coal molecule was believed to be a poly-aromatic structure, connected by aliphatic linkages.⁸ X-ray diffraction work later suggested alicyclic layers which were converted to graphitic layers as the coal rank increased.⁹ After the isolation of adamantane from a coal,¹⁰ a polyamantane structure, based on hypochlorite oxidation studies, was most recently proposed,¹¹ the alicyclic layers rearranging to aromatic platelets when the coal is heated.

Gasification

The conversion of coal to SNG is basically a two step process. In the first step, pretreated coal¹² is fed into a pressurized gasification reactor, where steam, O₂, and heat convert the coal to a mixture of CH₄, CO, CO₂, H₂, and H₂S:



This gas mixture has a calorific value of 150-350 Btu/ft³. Upgrading the gas by reaction with steam (4), followed by CO₂ and H₂S removal, yields a gas mixture (synthesis gas) of 400-500 Btu/ft³.



The small Lurgi and Koppers-Totzek reactors have found extensive commercialization in Europe.¹³ Reactors for the large scale use of bituminous coals have been developed, with the Hygas and CO₂-Acceptor processes approaching commercialization.¹⁴

Methanation

Final up-grading of the syn gas for high efficiency industrial and household use requires that the carbon oxides be hydrogenated to methane:^{4c}



Although supported metal catalysts have been used to hydrogenate trace amounts of CO and CO₂ to methane,¹⁵ more durable catalysts were needed for large scale reactions.¹⁶

Several Group VIII transition metals have been examined for catalytic activity.^{17,19} Although supported cobalt and ruthenium catalysts exhibit superior reactivity,^{18,20} Raney-nickel is the catalyst of choice for commercial use, due to its relative inexpense.^{18,21,22} The proposed reaction mechanism involves absorption on the gases onto the metal surface, followed by successive hydrogenations to methane.¹⁷ Preliminary methanation runs performed in pilot plants (1/200 full scale) yield a product gas of 94-99% methane,^{40,21} with a calorific value of 950-1000 Btu/ft³, the same as natural gas. Full commercialization of this final up-grading step is expected by 1980.

Economics

Even with the advanced state of coal methanation technology, the process is not inexpensive. Plant construction and minor costs for twenty 250 million ft³ CH₄/day plants is expected to exceed \$5 billion.²³ In the end, the consumer can expect to pay two to three times the current natural gas prices for SNG.

BIBLIOGRAPHY

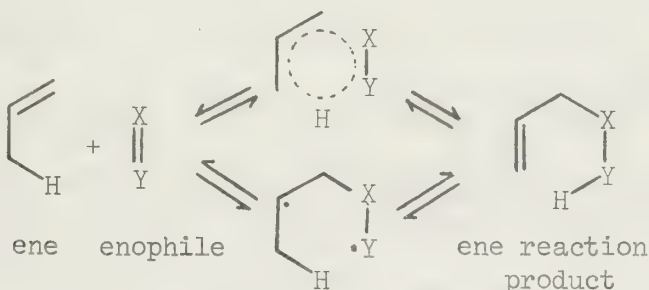
1. "The Efficient Use of Fuel", His Majesty's Stationary Office, London, 1944, pp. 3-6, 18.
2. A. W. Gauger, Physical Chemistry and Technology of Fuels", Edward Brothers, Ann Arbor, 1947, pp. 4, 8, 24, 35, 41.
3. M. E. Bailey, J. Chem. Educ., 51, 446 (1974).
4. a) J. P. Henry and B. M. Louks, Chem. Tech., 239 (1971); b) G. E. Klingman and R. P. Schaaf, Hydrocar. Process., 51 (4), 97 (1972); c) F. W. Moeller, H. Roberts and B. Britz, *ibid.*, 53(4), 69 (1974); d) H. Perry, Chem. Eng., July 22, 1974, pp. 88-94.
5. W. A. Bone and B. J. A. Bard, Proc. Roy. Soc., A, 162, 495 (1937).
6. R. S. Montgomery and E. D. Holly, Fuel, 35, 49, 56, 60 (1956); *ibid.*, 36, 63, 493 (1957).
7. J. Entel, J. Amer. Chem. Soc., 77, 611 (1955).
8. I. G. C. Dryden, Fuel, 34, S29 (1955).
9. S. Ergun, U. S. Bur. Mines Bull., No. 648, p. 35 (1968); Chem. Abstr., 70, 89440j (1969).
10. K. Imuta and K. Ouchi, Fuel, 52, 301 (1973).
11. S. K. Chakrabartty and N. Berkowitz, Fuel, 53, 240 (1974).
12. S. J. Gasior, A. J. Forney and J. H. Field, Ind. Eng. Chem., Prod. Res. Develop., 3, 43 (1964);
13. S. A. Bresler and J. D. Ireland, Chem. Eng., Oct. 16, 1972, pp. 103-108; M. G. Sheldrick, *ibid.*, July 12, 1971, pp. 59-61; Hydrocar. Process., 52(4), 124 (1973).
14. Chem. Eng., Oct. 14, 1974, p. 62.
15. W. W. Akers and R. R. White, Chem. Eng. Progr., 44, 553 (1948).
16. Chem. Eng. News, Sept. 16, 1974, p. 26.
17. G. A. Mills and F. W. Steffgen, Catal. Rev., 8, 159 (1973).
18. P. J. Lunde and F. L. Kester, Ind. Chem. Eng., Process. Des. Develop., 13, 27 (1974).
19. R. A. Dalla Betta, A. G. Piken and M. Schelef, J. Catal., 35, 54 (1974).
20. F. S. Karn, J. F. Shulz and R. B. Anderson, Ind. Eng. Chem., Prod. Res. Develop., 4, 265 (1965).
21. D. W. Allen and W. H. Yen, Chem. Eng. Progr., 69, 75 (1973).
22. J. H. Field, J. J. Demester, A. J. Forney and D. Bienstock, Ind. Eng. Chem., Prod. Res. Develop., 3, 50 (1964).
23. N. P. Chohey, Chem. Eng., April 3, 1972, pp. 44-46; Chem. Eng. July 22, 1974, pp. 58-60.

THE ENE REACTION: β -PINENE REACTIONS

Reported by Kenneth Berger

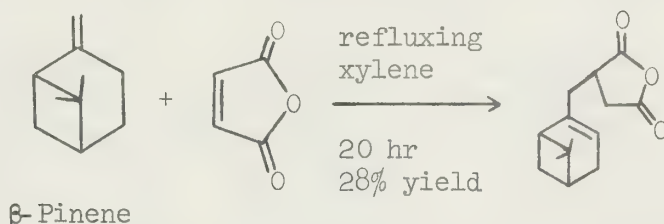
October 20, 1975

The ene reaction,¹ closely related to the Diels-Alder addition and [1,5] sigmatropic hydrogen shift, involves the thermal reaction of an ene, which is an olefin bearing an allylic hydrogen, with an electron-deficient enophile possessing a π bond.



Ene reactions can be high yield, synthetically useful reactions. For a comprehensive review of the ene reaction see the review by Hoffmann.¹

The mechanisms possible form a continuum with concerted, diradical, and ionic mechanisms at the extremes.^{1,2,3,4}



β -Pinene is a highly reactive olefin⁵ forming ene reaction products with the following enophiles: maleic anhydride,⁶ dimethyl maleate,⁵ fumarate,⁵ methylene malonic ester,⁵ formaldehyde,⁷ trichloroacetaldehyde,⁸ carbonyl cyanide,⁹ butyl glyoxylate,¹⁰ benzyne,^{11,12} singlet oxygen,¹³ methyl pyruvate,¹⁴ methyl phenyl glyoxylate,¹¹ and with lewis acid catalysts methyl acrylate and methyl vinyl ketone.¹⁵

The ene reaction appears to have some steric dependencies in that allylic hydrogens react in the order primary > secondary > tertiary (very slow).¹⁶ An orientation effect has been shown by Lambert and Napoli.¹⁷

For carbon-carbon π bond enophiles reacting with β -pinene it appears that the axial hydrogen is abstracted and that endo attack is preferred.^{6,11,14} Since no rearrangement products are isolated, it is concluded that the diradical or ionic mechanisms are not operative in the β -pinene system.

Some olefins may react with singlet oxygen by a mechanism outside the continuum described earlier and still yield products which would be expected for an ene reaction. Evidence is not as yet conclusive.^{13,18,19}

BIBLIOGRAPHY

1. H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 8, 556 (1969).
2. S. Dai and W. R. Dolbier, Jr., *J. Amer. Chem. Soc.*, 94, 3953 (1972).
3. H. A. Chia, B. E. Kirk, and D. R. Taylor, *Chem. Commun.*, 1144 (1971).
4. C. Agami, M. Andrac-Taussig, C. Justin, and C. Prevost, *Bull. Soc. Chim. Fr.*, 1195 (1966).
5. R. T. Arnold and J. S. Showell, *J. Amer. Chem. Soc.*, 79, 419 (1957).
6. R. K. Hill, J. W. Morgan, R. V. Shetty, and M. E. Synerholm, *ibid.*, 96, 4201 (1974).
7. J. P. Bain, *ibid.*, 68, 638 (1946); O. Brace, *ibid.*, 77, 4666 (1955).
8. M. Vilkas, G. Dupont, and R. Dulong, *Bull. Soc. Chim. Fr.*, 799 (1955).
9. G. I. Birnbaum, *Chem and Ind., London*, 1116 (1961).
10. E. I. Klimova and Y. A. Arbuzov, *Z. Org. Chim.*, 4, 1787 (1968).
11. V. Garsky, D. F. Koster, and R. T. Arnold, *J. Amer. Chem. Soc.*, 96, 4207 (1974).
12. G. Mehta and B. Pal Singh, *Tetrahedron*, 30, 2409 (1974).
13. C. S. Foote and R. W. Denny, *J. Amer. Chem. Soc.*, 93, 5162 (1971).
14. H. K. Spencer and R. K. Hill, *J. Org. Chem.*, 40, 217 (1975).
15. B. B. Snider, *ibid.*, 39, 255 (1974).
16. W. A. Thaler and B. Franzus, *ibid.*, 29, 2226 (1964).
17. J. B. Lambert and J. J. Napoli, *J. Amer. Chem. Soc.*, 95, 294 (1973).
18. C. S. Foote and R. W. Denny, *ibid.*, 93, 5168 (1971).
19. R. M. Kellogg and J. K. Kaiser, *J. Org. Chem.*, 40, 2575 (1975).

REACTIONS AND REARRANGEMENTS OF HEXAMETHYL(DEWAR BENZENE)

Reported by Lance A. Christell

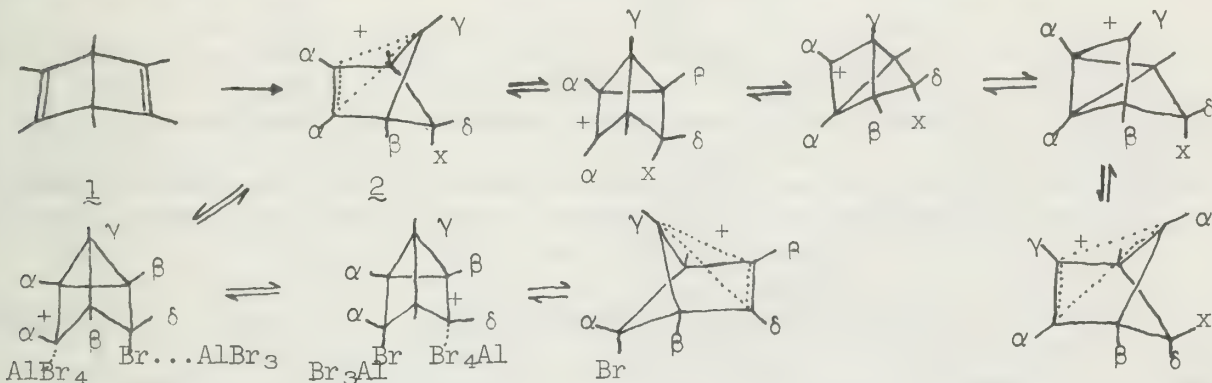
October 27, 1975

Since the postulation of the hexagonal structure for benzene in 1865, the synthetic chemist has been intrigued with its valence isomers, benzvalene: [3.1.0.0^{2,6}]tricyclohexene, and (Dewar)benzene; [2.2.0]bicyclohexadiene, and their reactions.¹ (Dewar)benzene is less stable than benzene by 60 kcal but the conversion has a high thermal activation energy due to orbital symmetry considerations. Although unsubstituted (Dewar)benzene has been synthesized,² and studied spectroscopically,³ the majority of reactions have been studied using hexamethyl(Dewar benzene), 1. Reactions with various reagents have been reported which yield a variety of mono-, di-, and tricyclic products.

When a solution of 1 is prepared with varying proportions of AlX₃ and the corresponding halogen at -78° in CD₂Cl₂, four methyl signals are observed corresponding to 2. As the solution is warmed in the probe the methyl signals coalesce at the indicated temperature.

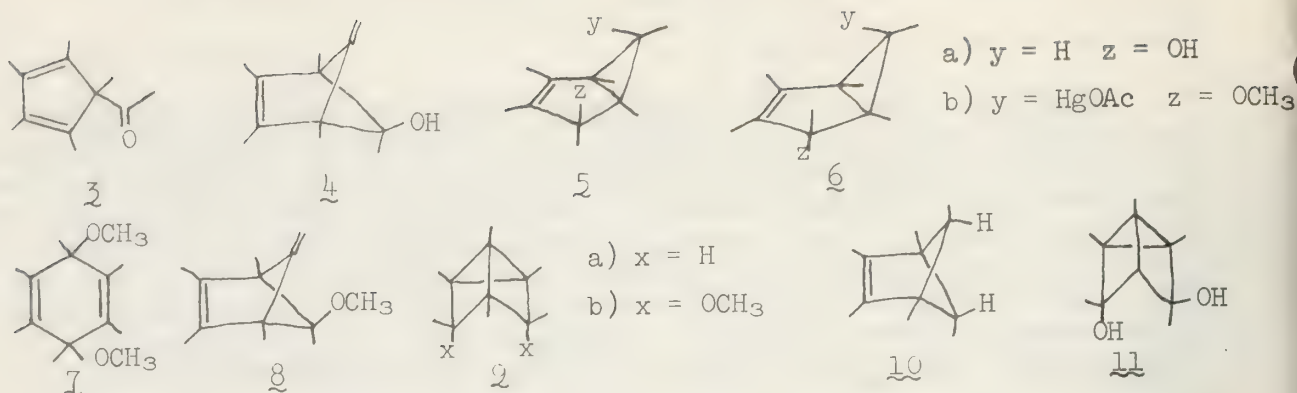
Ratio <u>1</u> :	AlX ₃ :	X ₂	Methyls	T _c
1.0	0.7	1.5	α, γ	35° ⁴
1.0	2.5	1.5	α, β, δ	-60° ⁵
			α, β, γ, δ	30°

The following reactions are suggested to account for the spectra.



Both endo and exo attack on 1 have been reported and rearrangements similar to the above have been helpful in explaining the products isolated. Exo attack is reported with the reagents: phenyl azide,⁶ buffered peracetic acid,⁷ and ethyl-N-sulphonyl carbamate.⁸ These all yield tricyclic products showing definite exo attack. The examples of endo attack by electrophiles are more numerous. Osmium tetroxide forms the endo-cis-diol readily.⁹ Positively charged electrophiles cause a rearrangement to form the endo-[2.1.1.]homoallylic-cyclohexenyl cation, 2.^{10a-h} In this intermediate the positive charge is concentrated on C2 and C3 according to cmr studies.¹¹

Product studies in different solvents yield a variety of reaction products. The Hg(OAc)₂ oxidation of 1 has been reported by Müller¹² and by Krow and Reilly.¹³ The latter reported the products for the reaction in THF as a 1:1 mixture of 3 and 4. They also noted the precipitation of Hg₀. Müller attempted to isolate an intermediate of the rearrangement so he ran the reaction for 10 sec followed by reduction of the oxymercureal with NaBH₄ in 10% NaOH. He isolated two isomeric products, 5a and 6a. These products indicate endo attack on 1. Further rearrangements led to the products. Müller also reported the reaction run in MeOH, and was able to isolate the oxymercureal intermediates 5b and 6b. Longer reaction periods in MeOH yield the products 7, 8, and 3.



A series of reactions has been reported by Hogeveen and Kwant which deserve attention.¹⁴ Reaction of 2 ($x = Br$) with LAH gives 9a. At -90° 10 is formed. Reaction with methoxide also forms the tricyclic derivative 9b. However when hydroxide is used compound 11 is formed. Hogeveen explains this by invoking a fast -OH isomerization after loss of bromide ion.

The use of optically active (Dewar)benzenes in reactions, such as the one reported by Wynberg *et al.*¹⁵ will help the interpretation of these reactions and the development of mechanisms to explain these and further reactions of (Dewar)benzenes.

BIBLIOGRAPHY

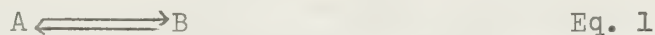
1. L. T. Scott, M. Jones, Chem. Rev., 72, 181 (1972); E. E. van Tamelen, Accts. Chem. Res., 5, 186 (1972); G. R. Brubaker, Org. Sem. Abst., 61 (1973).
2. E. E. van Tamelen, S. P. Papas, K. L. Kirk, J. Am. Chem. Soc., 93, 6092 (1971).
3. G. Bieri, E. Heilbronner, Tetrahedron Lett., 581 (1975); M. J. S. Dewar, S. Kirshner, Chem. Commun., 463 (1975); D. W. T. Griffith, J. E. Kent, Chem. Phys. Lett., 25, 290 (1974).
4. I. S. Isaev, V. I. Bureav, G. P. Novikov, L. M. Sosnovskaya, V. A. Koptug, J. Org. Chem. (USSR), 9, 2450 (1973).
5. H. Hogeveen, H. C. Volger, Rec. Trav. Chim., 87, 1042 (1968).
6. L. A. Paquette, R. J. Haluska, M. R. Short, L. K. Read, J. Clardy, J. Am. Chem. Soc., 94, 529 (1972).
7. W. Schafer, Angew. Chem., Int. Ed. Engl., 5, 669 (1966).
8. G. M. Atkins, Jr., E. M. Burgess, J. Am. Chem. Soc., 90, 4744 (1968).
9. G. R. Krow, J. Reilly, Tetrahedron Lett., 3129 (1972).
10. (a) L. A. Paquette, S. A. Lang, M. R. Short, B. Parkinson, J. Clardy, Tetrahedron Lett., 3141 (1972); (b) G. Mehta, N. Pattnaik, Ind. J. Chem., 11, 1313 (1973); (c) H. Hogeveen, P. W. Kwant, Tetrahedron Lett., 3197 (1972); (d) H. Hogeveen, H. Jorritsma, P. W. Kwant, Tetrahedron Lett., 1795 (1975); (e) H. Hogeveen, P. W. Kwant, Tetrahedron Lett., 3747 (1973); (f) H. Hogeveen, P. W. Kwant, J. Org. Chem., 39, 2624 (1974); (g) H. Hogeveen, P. W. Kwant, Tetrahedron Lett., 1351 (1973); (h) R. Hüttel, P. Tauchner, Tetrahedron Lett., 4733 (1972).
11. H. Hogeveen, P. W. Kwant, J. Am. Chem. Soc., 95, 7315 (1973).
12. E. Müller, Chem. Ber., 106, 3920 (1973).
13. G. R. Krow, J. Reilly, Tetrahedron Lett., 3133 (1972).
14. H. Hogeveen, P. W. Kwant, J. Thio, Rec. Trav. Chim., 93, 152 (1974); H. Hogeveen, P. W. Kwant, J. Am. Chem. Soc., 95, 7315 (1973).
15. H. Wynberg, J. H. Dopfer, B. Greigdanus, J. Am. Chem. Soc., 97, 216 (1975).

- 44 -
ANALYSES OF SOLVENT EFFECTS ON THE RELATIVE STABILITIES
OF ISOMERS WITH THE ONSAGER EQUATION

Reported by Johnny Covington

October 30, 1975

Many molecular systems have substantial differences in the relative energies of equilibrating isomeric forms in the gas phase and in solution. Chemists have sought to understand true energy differences both to gain a clearer understanding of the relative stabilities of different structural forms and to gain insight into the fundamental nature of solvent effects. In an ideal system the solvent effect can be understood in terms of the energies involved in an equilibrium between isomeric molecules A and B.



At equilibrium the standard free energy difference between these forms in solution is given by

$$\Delta G_{\text{soln.}}^{\circ} = -RT \ln K_{\text{soln.}} = -RT \ln \frac{\text{mole fraction of B.}}{\text{mole fraction of A}}$$

In the gas phase where concentration is expressed in terms of partial pressures (P_i) of A and B

$$\Delta G_{\text{gas}}^{\circ} = -RT \ln K_{\text{gas}} = -RT \ln \frac{P_B}{P_A}.$$

A formal definition of solvent effect then can be expressed in terms of Henry's law constant K_i^H as¹

$$\Delta \Delta G_{\text{solv. effect}} = \Delta G_{\text{soln.}} - \Delta G_{\text{gas}} = -RT \ln \frac{K_B^H}{K_A^H} \quad \text{Eq. 2}$$

In essence the Henry's law constants arise from differences in molecular energies in the gas phase and in solution due to hydrogen bonding, cavity formation, electrostatic interaction, etc. Understanding of the electrostatic terms of this solvation energy can be formulated in terms of solute and solvent properties such as dielectric constant and dipole moments.

Mathematical Formulation of Physical Models of Solvent Effects.

In 1936 one of the earliest physical models of the electrostatic term was provided by Onsager.² He developed an equation for the electric field which acts upon a rigid dipole of moment μ placed in the center of a spherical cavity of radius "a" in a medium of dielectric constant ϵ . The electric field, defined as R, which acts upon the dipole is a result of electrical displacement in the dielectric by the dipole and is called the reaction field. The reaction field is given mathematically as

$$R = \frac{2(\epsilon - 1)}{2\epsilon + 1} \frac{\mu}{a^3} \quad \text{Eq. 3}$$

From this, the solvation energy can be calculated

$$\Delta \Delta G_{\text{solv. effect}}^{\circ} = \Delta G_{\text{soln.}}^{\circ} - \Delta G_{\text{gas}}^{\circ} = \frac{(\epsilon - 1)}{(2\epsilon + 1)} \frac{(\mu^2)}{(a^3)}. \quad \text{Eq. 4}$$

About fifteen years later Bernstein and Powling³ defined "a" as the molecular radius of solvent and extended the equation to include the difference of two isomers

$$\Delta\Delta G_{\text{solv. effect}}^{\text{O}} = \left(\frac{\epsilon - 1}{2\epsilon + 1} \times \frac{\rho}{M} \right)_{\text{solv.}} (\mu_1^2 - \mu_2^2). \quad \text{Eq. 5}$$

Where, μ_1 is the electric moment of the less stable isomer and μ_2 that of the more stable isomer.
 ρ is the density of the solvent.
 M is solvent molecular weight.

More recently, Abraham⁴ further modified the equation to include solute polarization by its own reaction field. Abraham also included a quadrupole term. He claims that the exclusion of this term leads to predicted changes in energy which are about twice as high as observed.

Abraham also pointed out that previous experimentally determined solution energies have assumed that $\Delta G_{\text{soln.}}$ is independent of temperature. For example, when the relationship $K = e^{-\frac{\Delta G}{RT}}$ is used to calculate $\Delta G_{\text{soln.}}$ the implicit assumption is made that this energy is temperature independent. However, equation 5 shows that solvation energy is a function of solvent dielectric constant and density, both of which are temperature dependent. The experimentally determined $\Delta G_{\text{soln.}}$ then is actually some constant $(\Delta G_{\text{O}})_{\text{soln.}}$ which can be related to the true energy difference by

$$\Delta G_{\text{soln.}} = (\Delta G_{\text{O}})_{\text{soln.}} - T \frac{d(\Delta\Delta G)_{\text{solv. effect}}}{dt}$$

Abraham's equation is

$$\Delta\Delta G_{\text{solv. effect}} = -k' \rho x / (1 - 2r \rho x) + 3h' \rho x / 5 - x. \quad \text{Eq. 6}$$

Where, $x = (\epsilon - 1) / (2\epsilon + 1)$

ρ is the density of the medium

r is the specific refraction

$k' = k/\rho$ and $h' = h/\rho^{5/3}$

k and h are functions of the dipole and quadrupole
 q moments of the isomers and the molecular radius

$$k = k_A - k_B, \quad k_A = \mu_A^2 / a^3$$

$$h = h_A - h_B, \quad h_A = \sum_{i,j=x,y,z}^{i=j} [4q_{ii}^2 + (q_{ij}^2 + q_{ji}^2) - 4q_{jj}^2] / 2a^5.$$

The temperature dependence of $\Delta G_{\text{soln.}}$ can be evaluated if it is known how the density and dielectric constant of the pure liquid varies with temperature.

Perhaps the most far reaching theory of energy of solvation has been advanced by Sinanoğlu.¹ In this theory the process of taking a solute molecule from the gas to a fixed state in solution may be viewed as occurring in two steps. In the first step a hole is formed in the liquid and in the second step the molecule interacts with its new environment. For the reaction



the solvation energy $\Delta G_{\text{solv. effect}}^A$ is defined as

$$\Delta G_{\text{solv. effect}}^A = G_c^A - G_{\text{int.}}^A - RT \ln \frac{KT/P_0}{Ve} \quad \text{Eq. 7}$$

The term G_c^A is the energy required to make the cavity within the liquid and is related to the ordinary surface tension of the pure liquid. This term is derived from the thermodynamic properties of pure liquids and dilute solutions to give

$$G_c^A = K_e^e (\Phi_{1A}^{-\frac{1}{3}}) \times 4.836 V_A^{\frac{2}{3}} \gamma_1 (1 - W_{1A})$$

$$W_{1A} = (1 - \gamma_{1A}) \left(\frac{\partial \ln \gamma_1}{\partial \ln T} + \frac{2}{3} S_1 T \right)$$

Where, γ_1 is the surface tension of pure liquid 1

$$\gamma_{1A} = \frac{K_1^S (\Phi_{1A}^{-\frac{1}{3}})}{K_1^e (\Phi_{1A}^{-\frac{1}{3}})}$$

K_1^S and K_1^e are constants related to the entropy energy parts of G_c^A and depend on the volume fraction $\Phi_{2A} = \frac{V_2}{V_A}$

V_A is the average molecular volume of pure A in liquid form.

S_1 is the coefficient of thermal expansion of the solvent.

For polar solvents K_1^S in general will be different from K_1^e ,

if $K_1^S = K_1^e$ then $\gamma_{1A} = 1$ and W_{1A} vanishes, then

$$G_c^A = c V_A^{\frac{2}{3}} \gamma_1 \quad \text{where } c = K_1^e (\Phi_A^{-\frac{1}{3}}) \times 4.836 \quad \text{Eq. 9}$$

The second term in equation 6 is the free energy of interaction of molecule A with its new environment and includes a van der Waals (vdw) part which accounts for all the nonbonded, non-electrostatic attractions and repulsions. This term; G_{vdw}^A , is considered to be constant over a wide range of solvents so that

$$G_{vdw}^A = a \quad \text{Eq. 10}$$

The free energy of interaction also includes an electrostatic term which is essentially the equation arising from Onsager's reaction field

$$G_{e.s.}^A = \frac{1}{2} \frac{\mu_A^2}{a_A^3} D \times \frac{1}{(1-D) \frac{\alpha_A}{a_A^3}} + \text{higher multipoles}$$

Sinanoğlu assumed that the contribution made by G_{es}^A to the total solvation energy is relatively constant over a wide range of solvents. The solvent dependent part of G_{es}^A is found in D's which equals $\frac{2(\epsilon - 1)}{(2\epsilon + 1)}$; this term varies little from solvent to solvent. This gives G_{es}^A as

$$G_{es}^A = b \frac{\mu_A^2}{V_A} \quad \text{Eq. 12}$$

The last term in equation 6 is an entropy effect, roughly taking care of the "free volume" of A in the liquid whose average molecular volume is V_1 , $P = 1$ Atms. Combining equations 7, 9, 10, and 12 gives

$$\Delta G_A = a + b \left(\frac{\mu_A^2}{V_A} \right) - c V_A^{\frac{2}{3}} \gamma_1 - RT \ln \frac{KT}{V_1} \quad \text{Eq. 13}$$

$$\text{and } \Delta \Delta G_{\text{solv. effect}} = \Delta G_{\text{int}} + \Delta G_c + \Delta \left(RT \ln \frac{KT}{V_1} \right).$$

The reliability of the solvent effect models described can only be established by comparing the results obtained from them to experimental results. The theory as advanced by Onsager and extended by Bernstein and Abraham has been applied to a limited number of systems. The comparison of these calculated results to experimental results will be reported here. Also included is one case where Sinanoglu's theory was used.

The Effect of Solvent on Hindered Rotation

Langseth and Berstein⁵ investigated the rotational conformation of liquid 1,1,2,2-tetrachloroethane as a function of temperature by Raman spectroscopy. From the temperature of the intensities (I) of the lines between 100- 800 cm^{-1} the spectrum was separated into two spectra, one for the more stable isomer and one for the less stable isomer. The energy difference ΔG between the rotational isomers was calculated to be 1100 cal/mole using the equation

$$\frac{I_{\text{more stable isomer}}}{I_{\text{less stable isomer}} T_1} / \frac{I_{\text{more stable isomer}}}{I_{\text{less stable isomer}} T_2} = \exp. \frac{G}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right). \quad \text{Eq. 14}$$

Electron diffraction showed that the conformations were staggered.⁶ Thomas and Gwinn⁷ reported a value for ΔG of 0 ± 200 cal/mole in the gas phase from dipole moment measurements as a function of temperature and a consideration of C-Cl bond moments for a number of chlorinated compounds. The apparent anomaly between gas phase and liquid values is entirely due to environment in the liquid phase. Powling and Bernstein³ investigated the rotational equilibrium of dilute solutions of tetrachloroethane in bromine, carbon disulfide, stannic chloride, and tetrachloro ethylene by infrared spectroscopy. The relative intensities of the infrared bands 1279 cm^{-1} and 1243 cm^{-1} were temperature dependent. The band at 1279 cm^{-1} was assigned to the trans isomer which is less stable in solution and the band at 1243 cm^{-1} assigned to the skewed isomer which is more stable in solution.

The $\Delta G_{\text{soln.}}$ values determined from this study were plotted against

$\left(\frac{\epsilon - 1}{2\epsilon + 1} \right) \times \frac{\rho}{M}$ from equation 5. The plot, fig. 1, is a straight line, the slope of which is the dipole moment of the skewed isomer and the intercept is the energy difference in the gas phase. Powling and Bernstein³ calculated a ΔG_{gas} of 280 cal/mole using equation 5. Abraham⁴ reports a value of $\Delta G_{\text{gas}} = 200$ cal/mole using equation 6. The gas phase values from Onsager's Reaction field, eqs. 5 and 6

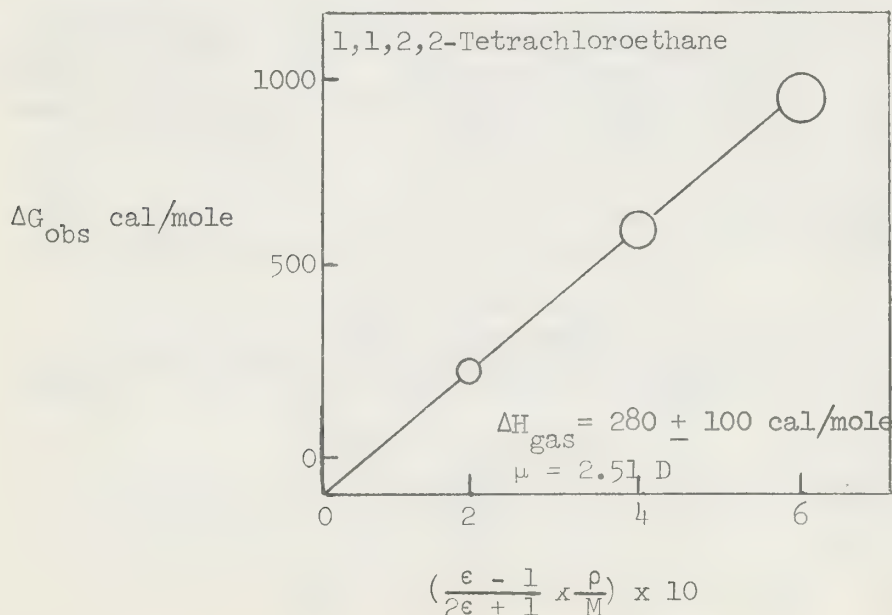


Fig. 1

compare with that reported by Thomas and Gwinn⁷ considering the experimental error reported by these authors. The inclusion of quadrupole terms in equation 6 tend to lower the calculated values of ΔG .

Hindered rotation has been studied extensively for 1,2-disubstituted haloethanes.

The two most stable conformations of 1,2-dichloroethane are trans and gauche forms. All gas phase measurements⁸⁻¹⁰ indicate that the trans isomer is more stable by 1300 ± 50 cal/mole but in the liquid¹⁰⁻¹² the energy difference between the trans isomer and the gauche isomer is zero. This leads to a solvation energy of about 1300 cal/mole in favor of the gauche form. The Onsager reaction field would predict that the gauche isomer would be stabilized relative to the trans form in solution since the gauche form has the larger dipole moment. Assuming $\mu_{\text{trans}} = 0$, Bernstein calculated $\mu_{\text{gauche}} = 2.53$ D using equation 5 which is in good agreement with 2.55 D calculated by Mizushima⁸ from dielectric constant measurements. The solvation energy of 1480 cal/mole calculated from equation 5 maybe too high due to the exclusion of quadrupole terms; however, considering the upper limit of the observed energy difference which is 1400 cal/mole¹⁰ this value may be within experimental error.

The liquid and gas phase energy difference for trans 1,2-dibromoethane and gauche 1,2-dichloroethane all favor the trans isomer but in solution the energy difference is about half the gas phase value. The experimental gas phase ΔG values range from 1770 - 1450 cal/mole^{13,14} and the experimental liquid ΔG value are 740 ± 500 cal/mole¹¹ and 760 cal/mole¹⁵. The calculated ΔG_{gas} values are 2000 equation 5³ and 1720 equation 6. The gauche form is stabilized relative to the trans form in solution but the electrostatic stabilization apparently is not enough to completely balance steric repulsion and the trans form is the most stable isomer in the liquid. The observed solvation energy for this compound, 790 cal/mole, can be compared to Abraham's calculated value of 970 cal/mole. This value while larger than the observed value is much smaller than 1340 cal/mole which is based on equation 5.

The energies of isomerization for 1-chloro-2-bromoethane are 1430 cal/mole ΔG_{gas} ,³ 450 cal/mole ΔG_{soln} .¹⁶ The calculated gas values are 1850 cal/mole, equation 5, and 1730 cal/mole, equation 6. Both isomers "trans" and "gauche" have dipole moments but that of the gauche form should be larger and the energy of the gauche form is lowered in solution relative to the trans isomer. Abraham's 1280 cal/mole solvation energy again is closer to the observed of 980 cal/mole value than Bernstein's value of 1400 cal/mole indicating that the quadrupole term is important for these calculations.

Abraham and Eliel³⁴ studied the equilibrium of the cis-trans configurations of 5-heterosubstituted-2-isopropyl-1,3-dioxanes as a function of solvent polarity.

The ring dipole and substituent dipole are involved in electrostatic repulsion in the cis configuration whereas a slightly attractive interaction might be expected for the trans configuration. The experimentally determined ΔG_{soln} value are listed in Table I also listed are the calculated values using equation 6. There is good agreement between calculated and the observed values. The large solvent effect on these systems can be completely explained by this theory.

The Effect of Solvent on Tautomeric Equilibrium

Bernstein³⁸ calculated ΔH for the keto-enol tautomers of acetylacetone from the temperature dependence of the two C=O bands near 1725 and 1625 cm^{-1} in the infrared. ΔH values were calculated for the gas phase and solutions of acetylacetone in decalin, tetrachloroethylene and bromoform. These values were

plotted against the term $(\frac{\epsilon - 1}{2\epsilon + 1} \times \frac{\rho}{M})_{\text{soln}}$ to give a gas phase enthalpy of

TABLE I

Calculated and Observed Energy Differences (Kcal/mole) for
5-Substituted-2-Isopropyl-1,3-dioxanes

Solvent	X = F		X = Cl		X = Br		X = OMe	
	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd
Vapor	0.6		2.2		2.5		1.25	
CCl ₄	-0.37	-0.36	1.41	1.40	1.75	1.71	0.80	0.90
Et ₂ O	-0.78	-0.62	0.90	1.26	1.26	1.45	0.47	0.83
CHCl ₃	-0.84	-0.87	0.85	0.94	1.21	1.35	0.43	0.16
CH ₃ CN	-1.43	-1.22	0.29	0.25	0.68	0.68	0.08	-0.01

2.4 Kcal/mole which is the observed value. Grossman²⁴ measured the heat of tautomerization of ethyl acetoacetate in the solvents listed in Fig. 2, Bernstein's³⁶ plot of these values against $(\frac{\epsilon - 1}{2\epsilon + 1} \times \frac{\rho}{M})_{\text{solv.}}$. The point for hexane, carbon tetrachloride and ether all lie on a straight line and extrapolate to a gas phase enthalpy of 2.0 Kcal/mole. The ΔH values in alcoholic solvents extrapolate to approximately the same gas values but the slope of the line is less than the slope for the nonpolar solvents. It may be that solvent-solute hydrogen bonding would account for this difference.

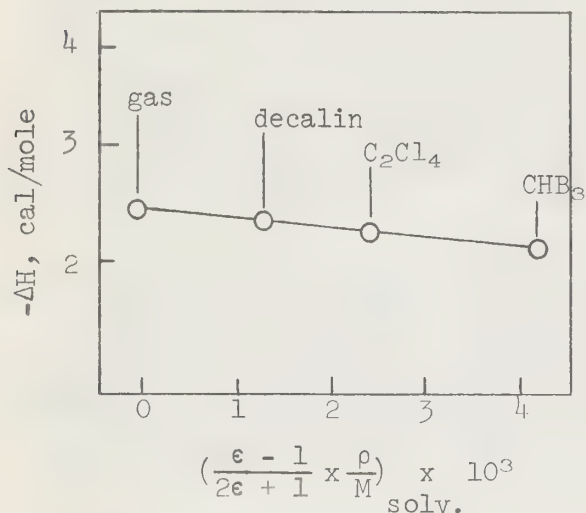


Fig. 2 - Acetylacetone

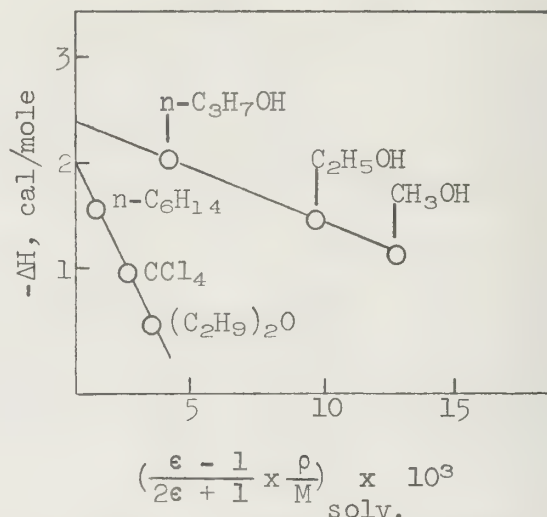


Fig. 3 - Ethylacetoacetate

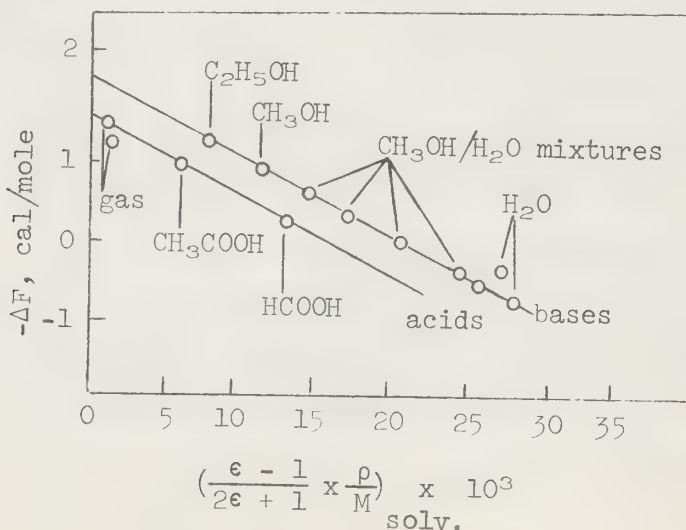


Fig. 4 - Acetylacetone

In Fig. 4 the change in free energy of the tautomeric equilibrium of acetylacetone in a series of basic and acidic solvents is plotted against $(\frac{\epsilon - 1}{2\epsilon + 1} \times \frac{\rho}{M})$. Even for these polar solvents straight lines are obtained both of which extrapolate to a fair measure of the gas phase value (to within 0.2-0.3 Kcal/mole). It would appear that the two lines are parallel in Fig. 4. However, a careful study of the remaining plots Fig. 5-7, where acid values lie on the same line as

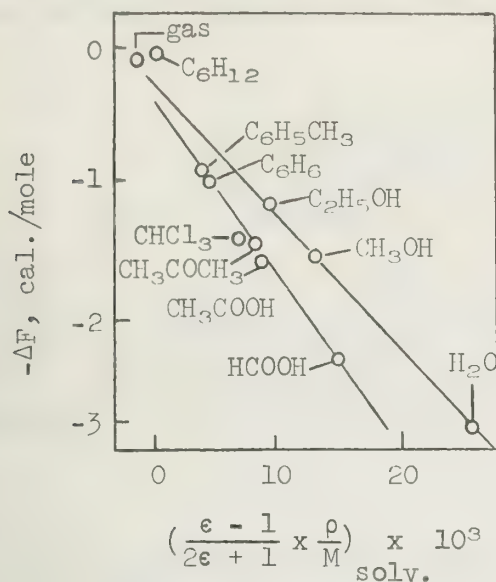


Fig. 5 - Ethyl acetoacetate

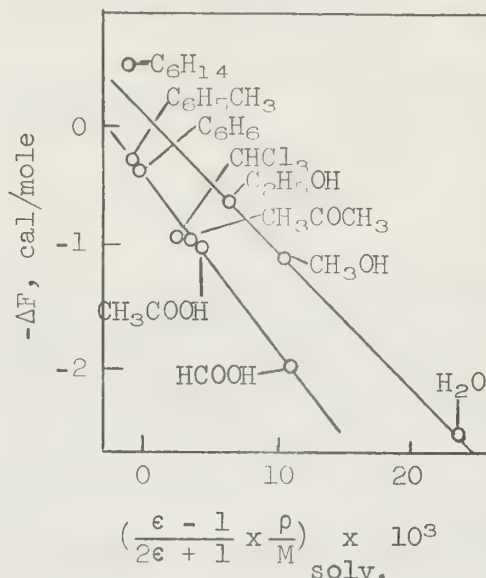


Fig. 6 - Methyl benzoylacetate

the relatively nonpolar solvents and with a different slope than those values in basic solvents, may indicate that acid values in Fig. 4 are too high. The plots in Figs. 4-7 suggest that the acidic solvents studied have no effect on tautomeric equilibrium except those accounted for by Onsager's reaction field and are linear to those effects in non polar solvents. The acid molecules may favor hydrogen bonding with other acid molecules rather than with the tautomers.

The equilibrium of 2-hydroxypyridine(11)-2-pyridone (12) has been studied in aqueous solution where basicity measurements with 13 and 14 as model compounds provided a value of the free energy difference of about 4.1 Kcal/mole in favor of 12.³² Beak and Fry³³ investigated the equilibrium in the gas phase and report a value of ΔG at 132° of 0.8 Kcal/mole. They also showed that the equilibrium is essentially temperature independent over the range 120-350°. Noting this temperature independence the equilibrium was studied in decane as a function of temperature. From 25 to 130 the spectrum was observed to change, the absorbance of 11 increased over this range and the absorbance of 12 decreased. At temperatures between 130-155° no change was observed. If at 130° all species in solution are monomeric then the observed equilibrium

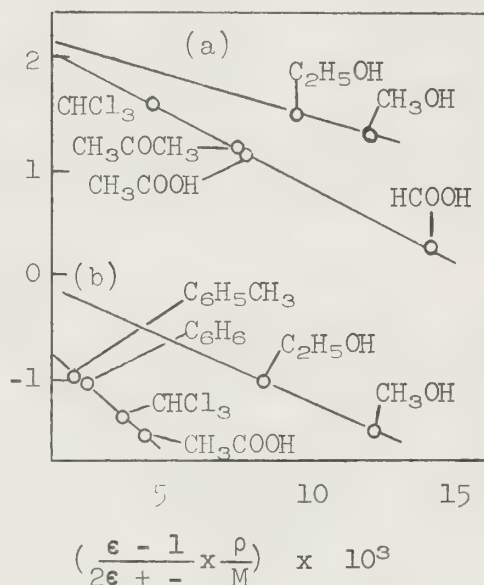
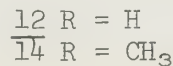
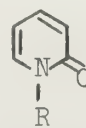
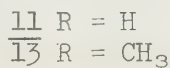
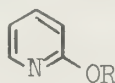
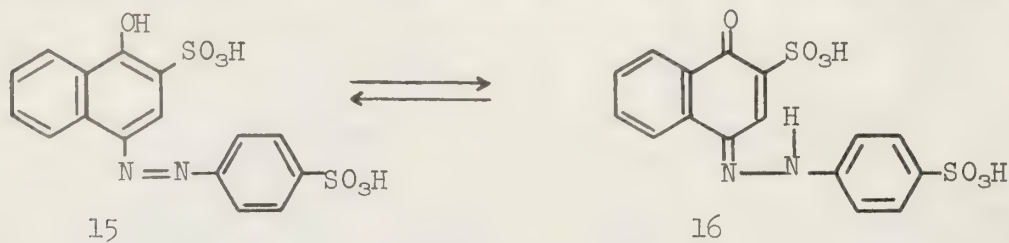


Fig.

Fig. 7 - (a) Benzoylacetone
(b) Acetoacetanilide

gives a ΔG^0 value of .39 Kcal/mole. The observed energy of solvation $\Delta\Delta G$ for 11-12 $\Delta G_{\text{soln.}} - \Delta G_{\text{gas}}$ is 5 Kcal/mole when the solvent is water and 1.2 Kcal/mole when the solvent is decane; the calculated values, equation 5, are 5 for water and 1.4 Kcal/mole for decane. Those values calculate from equation 5 are very close to the observed values.

Reeves and coworkers investigated the equilibrium of 15 and 16 in a series of hydrogen bonding solvent. They find no correlation between solvent polarity



as defined by Onsager and the equilibrium constant (K_T) for these solvents. Further the best correlation was between cavity surface energy and K_T in support of the Sinanoğlu theory. Reeves suggests that in order for cavitation to the solvation energy between two isomers, the isomers must respond differently to changes in cavity surface energy.

Summary

The application of the Onsager reaction field to hindered rotation and tautomeric equilibrium have been reviewed. The results to date indicate that the theory provides a suprisingly good measure of the effect of solvent on these processes. In applying Onsager's equation to tautomeric equilibrium other effects such as solvent-solute associations must be accounted for. Onsager's equation tends to break down in polar solvents. This may be due to the absence of dipole-dipole interaction terms and may account for Reeves results. Sinanoğlu's assumption concerning the constancy of the electrostatic term ΔG_{es} is an over simplification. However, no conclusions can be reached concerning the importance of cavitation from the cases reviewed here. Further work is needed before a final verdict is reached as to the importance of the Onsager theory to equilibrium in general.

BIBLIOGRAPHY

1. O. Sinanoğlu in "Molecular Associations in Biology", E. B. Pullman, Ed., Academic Press, New York, N. Y., 1967, p 427.
2. L. Onsager, J. Amer. Chem. Soc., 53, 1486 (1936).
3. J. Powling and H. J. Bernstein, J. Amer. Chem. Soc., 75, 1815 (1951).
4. R. J. Abraham, Molecular Physics, II, 471 (1966).
5. Langseth and Bernstein, J. Chem. Phys., 8, 410 (1940).
6. A. Turhevich and J. Y. Beach, J. Amer. Chem. Soc., 61, 3127 (1939).
7. W. D. Gwinn and J. R. Thomas, J. Amer. Chem. Soc., 71, 2785 (1949).
8. I. Watamaba, S. Mizushima and Y. Marino, Sci. Pop. Inst. Phys. Chem. Res. (Tokyo), 39, 401 (1942).
9. H. J. Bernstein, J. Chem. Phys., 17, 256 (1943).
10. W. D. Gwinn and K. S. Pitzer, J. Chem. Phys., 16, 303 (1948).
11. D. H. Rank, R. E. Kagaine and D. W. E. Axford, J. Chem. Phys., 17, 1354 (1949).
12. H. Gerding and P. C. Mccrman, Rec. Tran. Chem., 61, 303 (1948).
13. T. Simonontu, H. Turnter and S. Mizushima, Sci. Pop. Inst. Phys. Chem. Res. (Tokyo), 42, 165 (1945).
14. H. J. Bernstein, J. Chem. Phys., 18, 897 (1950).
15. Mizushima, Mareno, Kuratunic and Katagana, J. Chem. Phys., 18, 754 (1950).
16. N. Sheppard, Adv. Spectroscopy, 1, 288 (1959).
17. R. J. Abraham and M. A. Cooper, Chem. Comm., 588 (1966).

18. R. J. Abraham and M. A. Cooper, J. Chem. Soc., B, 202 (1967).
19. R. J. Abraham, K. G. R. Pochler, and P. L. Wessels, Z. Phys. Chem., 58, 257 (1968).
20. R. J. Abraham, J. Phys. Chem., 73, 1192 (1969).
21. Mizushima and Marino, Sci. Pop. Inst. Phys. Chem. Res. (Tokyo), 29, 188 (1936).
22. Mizushima and Kozina, Sci. Pop. Inst. Phys. Chem. Res. (Tokyo), 31, 296 (1937).
23. Watonabe, Mizushima and Masiko, Sci. Pop. Inst. Phys. Chem. Res. (Tokyo), 40, 425 (1943).
24. Grossman, Z. Phys. Chem., 109, 304 (1924).
25. K. H. Meyer and P. K. Appelmeier, Ber., 44, 2718 (1911).
26. K. H. Meyer, Ber., 45, 2843 (1912).
27. K. H. Meyer, Ber., 47, 826 (1914).
28. K. H. Meyer and F. G. Wilson, Ber., 47, 832 (1914).
29. W. Gordy, J. Chem. Phys., 8, 516 (1940).
30. R. S. Rassmussen, D. D. Tunnicliffe and R. R. Brattain, J. Amer. Chem. Soc., 71, 1068 (1949).
31. D. N. Shigorin, Zhur. Fiz. Him., 23, 506 (1949).
32. M. J. Cook, A. R. Katritzky, P. Linda and R. D. Tack, J. Chem. Soc., Perkin Trans., II, 1295 (1972).
33. P. Beak and F. S. Fry, J. Amer. Chem. Soc., 95, 1200 (1973).
34. R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaloustian, J. Amer. Chem. Soc., 94, 1913 (1972).
35. R. L. Reeves, M. S. Maggio, and L. F. Costa, J. Amer. Chem. Soc., 96, 5917 (1974).
36. J. Powling and H. J. Bernstein, J. Amer. Chem. Soc., 73, 4353 (1951).

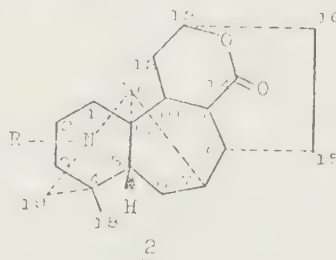
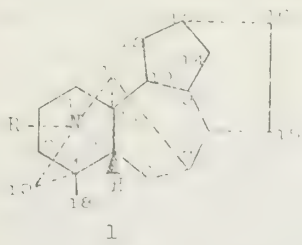
STRUCTURE AND SYNTHESIS OF C₁₉-DITERPENE ALKALOIDS

Reported by Mark W. Johnson

November 3, 1975

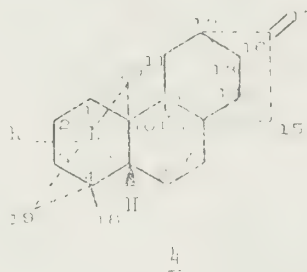
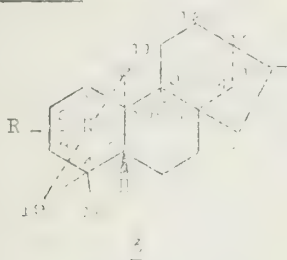
Diterpene alkaloids have been of interest for many years because of their pharmacological properties and complex structures. They have been isolated from plants of Aconitum and Delphinium genera of Ranunculaceae, the Garrya genus of Garryaceae and Inula royleana of the Compositae.

The diterpene alkaloids can be divided into two classes: a) the "aconitines" which are based on a hexacyclic C₁₉-skeleton and b) those based on a C₂₀-skeleton. The aconitines are highly oxygenated ester bases that possess either the lyco-tonine (1) or the heteratisine (2) skeleton. These highly toxic compounds were



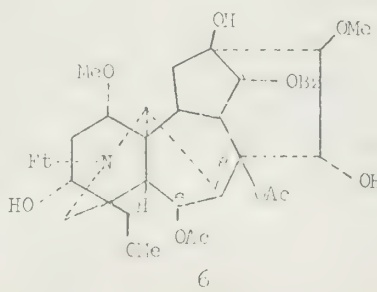
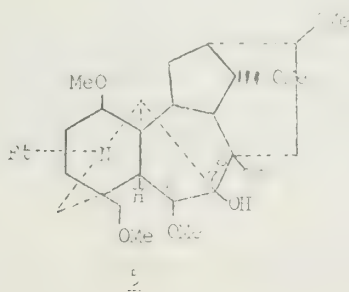
the active principles of many poisonous extracts used in medieval trials by ordeal. Two of the compounds in this group, aconitine and pseudoaconitine, are among the most toxic compounds of plant origin yet isolated. Upon hydrolysis the aconitines yield relatively non-toxic parent alkalamines known as "aconines".^{1a}

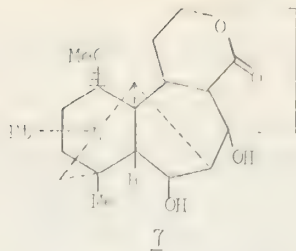
The class of diterpene alkaloids based on a C₂₀-skeleton are not as highly oxygenated as the aconitines and are relatively non-toxic. They are based on either the veatchine (3) or the atisine (4) skeleton. The Garrya alkaloids possess the isoprenoid kaurene-type veatchine skeleton. The atisine skeleton is found in alkaloids isolated from Aconitum and Delphinium species and from Spiraea japonica.^{1a}



Structural and Chemical Investigations

The C₁₉-diterpene alkaloids can be further subdivided into three general types: lycoctonine (5), aconitine (6), and heteratisine (7), which are based on the parent alkaloid of the same name. Whereas the hydroxyl group at C-8 is common to all C₁₉ diterpene alkaloids isolated thus far, the presence of an oxygen function at C-7 is peculiar to lycoctonine-type alkaloids. The C-7 to C-8 α-glycol in the lycoctonine-type alkaloids is responsible for the difference in the chemistry of these alkaloidal types.



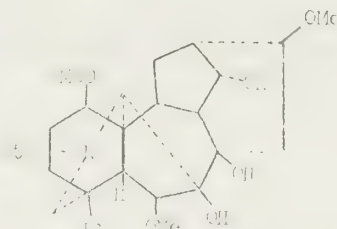


The heteratisine-type lactone alkaloids make up a very small fraction of the total alkaloidal content in the various plant species. The structures of the other members of this class are somewhere between the lycoctonine-type alkaloids and the parent lactone, heteratisine.^{1a}

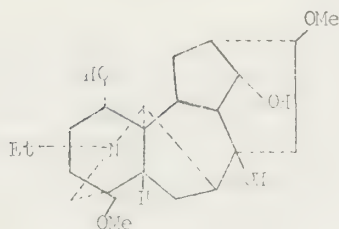
Lycoctonine-Type Alkaloids

The lycoctonine alkaloids are characterized by a high degree of oxygenated substituents, usually five or six, and although a great deal of effort was made, the structure completely eluded determination by chemical means. The structure of lycoctonine was finally solved by x-ray crystallography in 1956.²

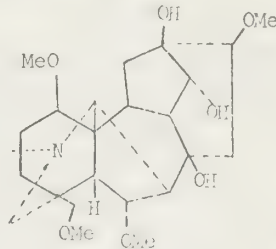
Jones and Benn have demonstrated the important contribution of ^{13}C nmr to the structure elucidation of diterpenoid alkaloids.³ The cmr spectra reveal not only the number and type of carbon atoms in the system, but also exhibit close structural and "family" resemblances and indicate the degree and sites of oxygen substitution. All carbon resonances are found in the region 10-100 ppm downfield from tms. In this particular study Jones and Benn examined the ^{13}C nmr spectra of lycoctonine (8), deoxylycoctonine (9), deoxymethylenelycoctonine (10), line (11), isotalatizidine (12), delphonine (13), lycoctonal (14), and their corresponding hydrochloride or perchlorate salts using decoupling techniques and additivity relationships.³



Lycoctonine (8)	$\text{R}^1 = \text{CH}_2\text{OH}; \text{R}^2 = \text{Me}$
Deoxylycoctonine (9)	$\text{R}^1 = \text{R}^2 = \text{Me}$
Deoxymethylenelycoctonine (10)	$\text{R}^1 = \text{H}; \text{R}^2 = \text{Me}$
Line (11)	$\text{R}^1 = \text{CH}_2\text{OMe}; \text{R}^2 = \text{H}$
Lycoctonal (14)	$\text{R}^1 = \text{CHO}; \text{R}^2 = \text{Me}$



Isotalatizidine 12

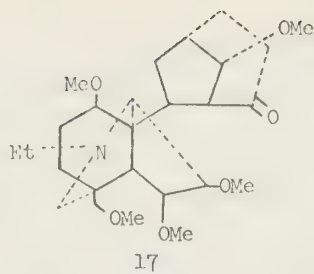
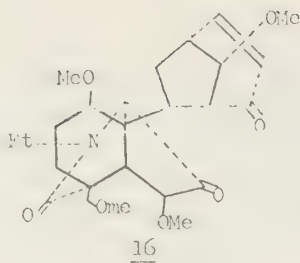
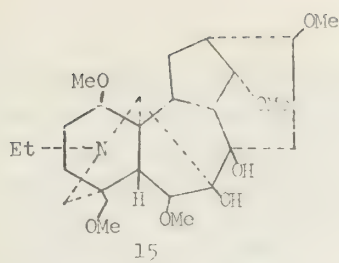


Delphonine 13

For these alkaloids ^{13}C shifts of 50 ppm downfield were common for the heteroatom-substituted carbons, while those for carbons that were not substituted with heteroatoms were in most cases upfield. The shifts of the quaternary carbon atoms were in a constant pattern except in cases of major substitution differences.³

Delphatine ($\text{C}_{26}\text{H}_{43}\text{NO}_7$)

This alkaloid from Delphinium biternatum was assigned structure (15) by Yunusov and Yunusov on the basis of spectral and chemical data.⁴ Oxidation to



a lactam by permanganate (KMnO_4 , aq. acetone), cleavage by periodic acid, and treatment with acid gave a desmethanolsecodiketone (16). Hydrogenation of this over Adams' catalyst followed by methylation gave a product (17) which was identical with a compound produced in the same way from lycoctonine. Mass-spectral comparison of delphatine and its derivatives with lycoctonine (8), browniine (11), and their derivatives indicated that there were methoxyl groups at C-6 and C-18 in delphatine.

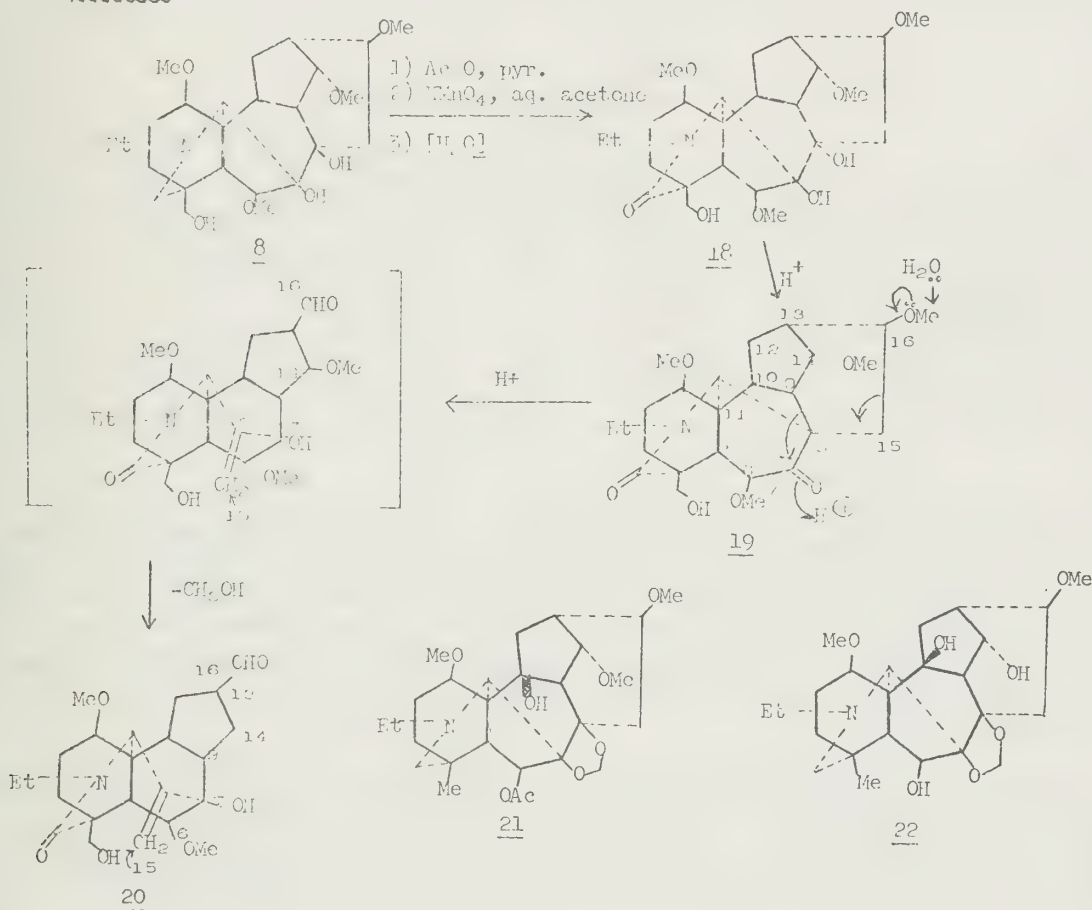
Lycoctamone

Among the most unusual aspects of lycoctonine chemistry is the rearrangement of the lactam (18), as shown in Scheme 1, to lycoctamone (20). Since several carbon atoms become readily accessible in lycoctamone and its analogues from related alkaloids, they may be useful in biosynthetic studies.⁵

Deltaline and Dictyocarpine

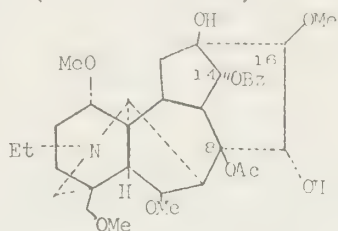
Yunusov and co-workers^{6,7} have isolated deltaline (21) and dictyocarpine (22), two 7,8-methylenedioxy-bridged lycoctonine-type alkaloids, from Delphinium dictyocarpum. Another unique feature of these alkaloids is the hydroxyl group at C-10.

Scheme 1

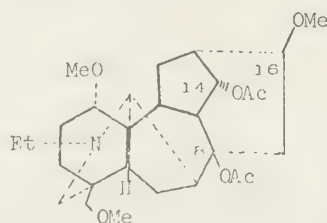


Aconitine-Type Alkaloids

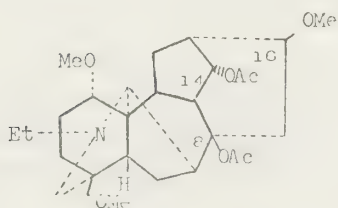
A characteristic feature of aconitine-type alkaloids with an acetoxy group at C-8 is the extreme ease of elimination of a mole of acetic acid. This process also accompanies mass-spectrometric decomposition. The relative ease of pyrolysis is dependent upon temperature and the size of the substituents at C-8, C-14, and C-16. The larger the substituents, the easier the pyrolysis. This is explained by the fact that the substituents at C-8, C-14, and C-16 are all axial and rather crowded together. The fact that this crowding is relieved through the pyrolysis is an added driving force for the reaction. The relative ease of pyrolysis can be followed by comparing the intensities of the M-AcOH and M-AcO peaks (see Table 1.).⁸



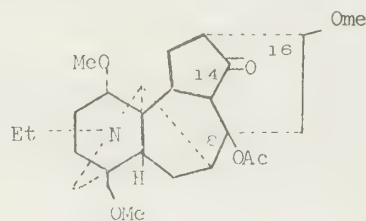
Aconitine I



Acetylbenzoyltalatisimine II



Diacetylaltalatisimine III



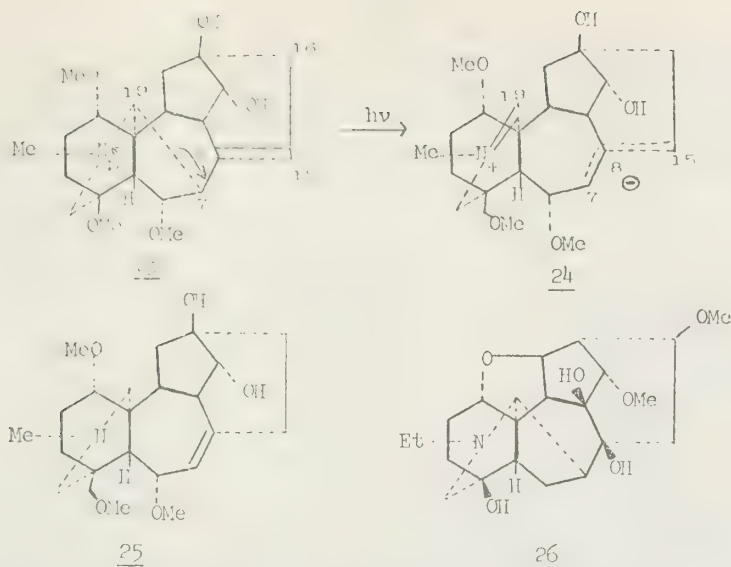
Dehydroacetylaltalatisimine IV

Table 1.

Ions	Relative intensity %					
	I (125°)	II (110°)	III (125°)	III (70°)	IV (105°)	IV (75°)
M	---	0.1	2	3.5	3.5	6
M-OCH ₃	---	0.3	100	100	100	100
M-AcOH	6	40	22	7	6	5
M-AcOH-OCH ₃						
M-OCH ₃ -AcOH	100	100	33	19	22	14
M-AcO-CH ₃ OH						
M-AcO	1	6	14	10	16	16

Another characteristic of aconitine-type alkaloids is the apparent diene chromophore in pyrolyzed alkaloids (or "pyro" compounds) which disappears upon acidification. The "pyro" chromophore was first observed⁹ in 1952, but it was not until 1960 that an explanation was proposed.¹⁰ Wiesner postulated the participation of the free electron pair on nitrogen, the C-7-C-19 σ -bond, and the π -system of the double bond between C-8 and C-15, with an excited state possibly resembling 24.

In an attempt to trap this excited state by reduction of the immonium ion (24),¹¹ 16-desmethoxy pyrodelphonine (23) was photolyzed in methanol in the presence of sodium borohydride, giving the 7,17-seco-olefin (25). When sodium borodeuteride was used, one deuterium atom was incorporated into (25). Thus, Wiesner's postulate seems to have been verified.

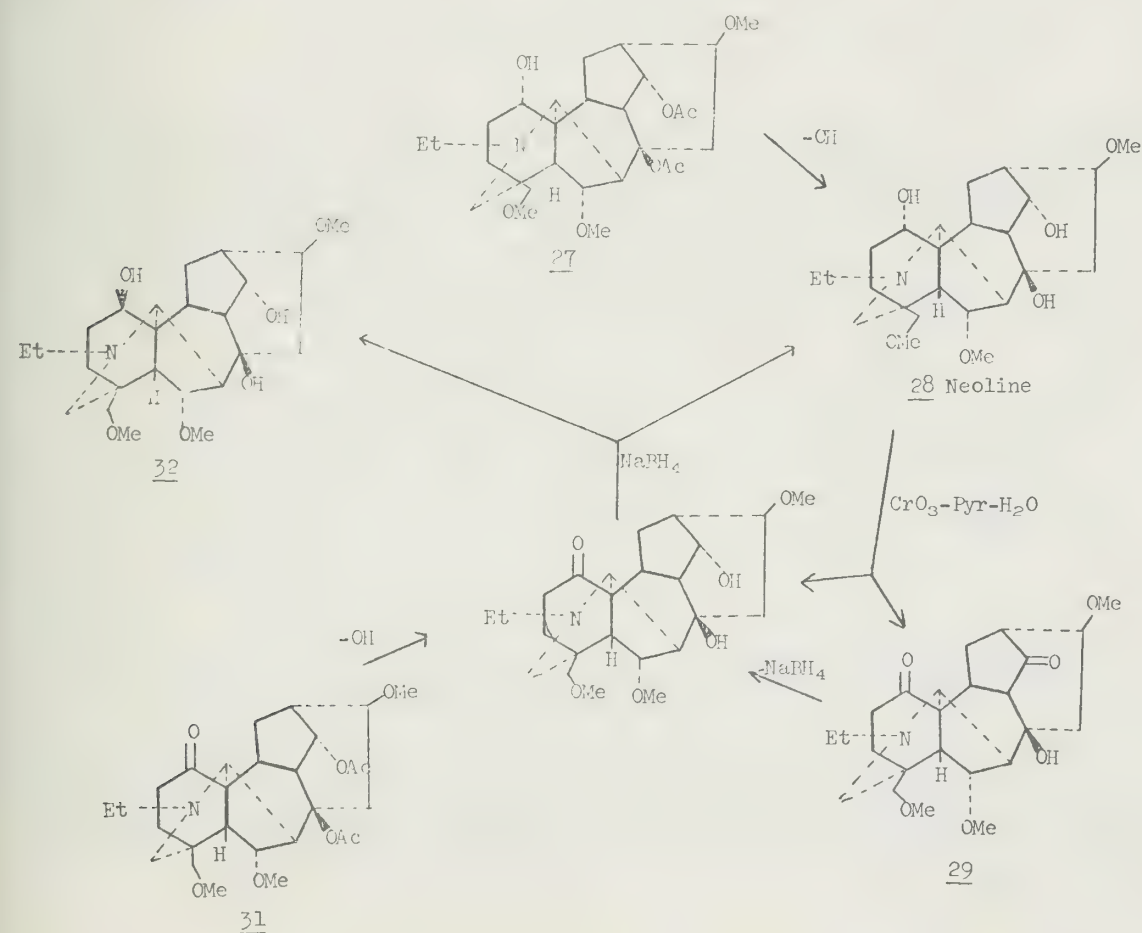


Excelsine

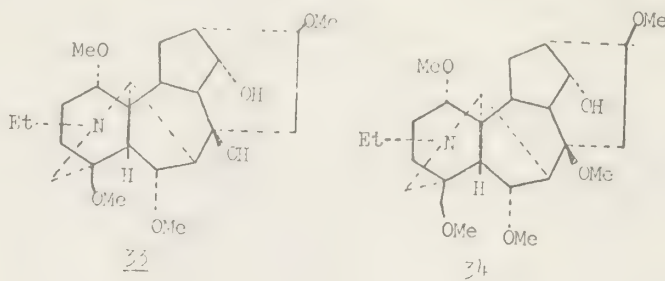
Yunusov and co-workers¹² have isolated excelsine from *Aconitum excelsum* and have proposed (26) as the structure based on chemical and spectral data. Model studies indicated that an oxygen bridge between C-1 and C-6 is improbable; therefore, an ether linkage between C-1 and C-12 was proposed.

Delphisine

Pelletier and co-workers¹³ have recently isolated delphisine, a new diterpene alkaloid, from *Delphinium staphisagria*. Spectral and chemical evidence have identified it as a member of the aconitine group of alkaloids. The molecular structure and absolute configuration were established as (27) by an x-ray crystallographic study of delphisine-hydrochloride.¹³

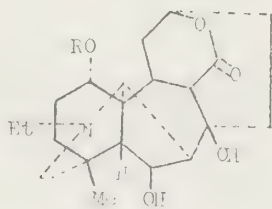


Pelletier has also correlated the structure of delphisine with those of neoline, chasmanine (33), and homochasmanine (34).¹⁴ Delphisine has, by three routes, been converted to a pair of C-1 epimers (Scheme 2). Mild hydrolysis of delphisine yields epimer (28) which is identical with neoline.

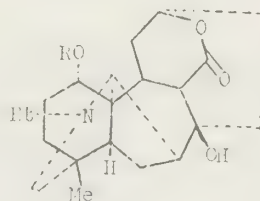


Heteratisine-type Alkaloids

Heteratisine (35), heteraphyllisine (36), heterophylline (37), and heteraphyllidine (38) are C₁₉-diterpene alkaloids occurring in the mother liquors of *Aconitum heterophyllum*. The structure of heteratisine was elucidated by x-ray diffraction techniques,¹⁵ and by chemical and spectral analyses.^{16,17} Heterophylline, heteraphyllisine, and heteraphyllidine were isolated from heteratisine mother liquors.^{18,19}



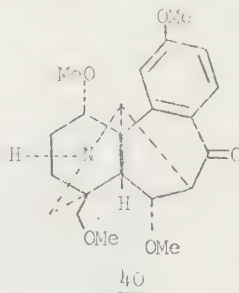
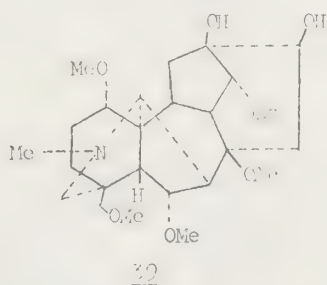
Heteratisine 35 R = Me
Heteraphyllidine 38 R = H



Heteraphyllisine 36 R = Me
Heterophylline 37 R = H

Synthetic Approaches

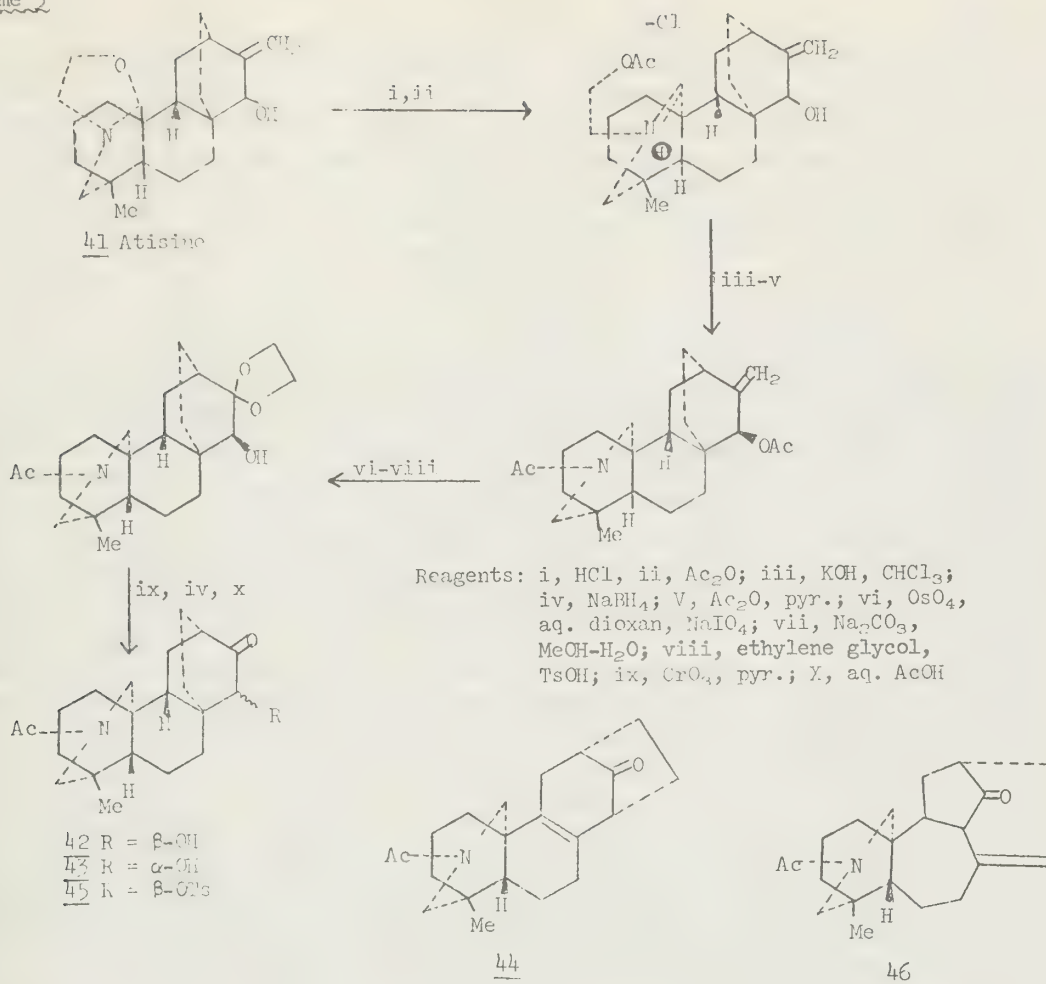
Wiesner and co-workers have expended considerable effort toward the synthesis of delphinine (39) and other alkaloids of this type.^{20a-d} They have succeeded in completing the synthesis of the aromatization product (40) which was originally obtained in high yield from the degradation of delphinine.^{20c}



Johnson and Overton have approached the synthesis of aconitine alkaloids through the conversion of the atisane skeleton into the aconitine skeleton by utilizing reactions to effect a key step in a proposed biogenetic pathway.²¹

Atisine (41) was converted into the epimeric ketols (42) and (43) as outlined in Scheme 3. Acetolysis of (42) or (43) gave only (44). However, pre-parative gas-phase pyrolysis of the β -tosylate (45) afforded the desired keto-olefin (46) in 77% yield.

Scheme 3



Wiesner and co-workers have developed an annelation procedure for the construction of the A-ring system in diterpenoid systems.²² They have also investigated a new synthetic route for the construction of the C/D ring system of delphinine-type alkaloids in a model series based on previous syntheses of the atisine system.²³

The first formal total synthesis of a delphinine-type alkaloid, talatisimine (48), has been completed by Wiesner and co-workers²⁴ starting from compound (47).



Wiesner's group has recently developed a more efficient method for the construction of delphinine-type alkaloids via the rearrangement of substituted demudatine derivatives.²⁵ Model studies currently in progress are directed toward the use of this more efficient route in the synthesis of chasmanine (49).

Conclusion.

The C_{18} -diterpene alkaloids that have been discussed here are only a representative sample of the members of this group of alkaloids. As can be seen from this review much emphasis in work related to diterpenoid alkaloids has been directed toward structure elucidation. However, this emphasis should be shifting more and more towards partial and total synthesis in the future as model studies now in progress are completed.

BIBLIOGRAPHY

1. (a) S. W. Pelletier, MTP Int. Rev. Sci.: Org. Chem., Ser. One, 1973, Vol. 9, p. 319. For other recent reviews see: (b) O. E. Edwards, Specialist Periodical Reports: The Alkaloids, 1, 343 (1971); (c) S. W. Pelletier and L. H. Wright, Specialist Periodical Reports: The Alkaloids, 2, 247 (1972); (d) S. W. Pelletier and S. W. Page, Specialist Periodical Reports: The Alkaloids, 4, 323 (1974).
2. M. Przybylska and L. Marion, Can. J. Chem., 34, 185 (1956).
3. A. J. Jones and M. H. Benn, Can. J. Chem., 51, 486 (1973).
4. M. S. Yunusov and S. Yu. Yunusov, Khim. Prir. Soedin., 6, 334 (1970), English translation.
5. M. H. Benn, J. D. Connolly, O. E. Edwards, L. Marion, and Z. Stojanac, Can. J. Chem., 49, 425 (1971). See also R. C. Cookson and M. E. Trevett, J. Chem. Soc., 3864 (1956).
6. A. S. Narzullaev, M. S. Yunusov, and S. Yu Yunusov, Khim. Prir. Soedin., 8, 498 (1972), English translation.
7. A. S. Narzullaev, M. S. Yunusov, and S. Yu Yunusov, Khim. Prir. Soedin., 7, 626 (1971), English translation.
8. M. S. Yunusov, Ya. V. Rashkes, and S. Yu. Yunusov, Khim. Prir. Soedin., 7, 626 (1971), English translation.
9. O. E. Edwards and L. Marion, Can. J. Chem., 30, 627 (1952).
10. K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Babin, F. Bickelhaupt, J. Kallas, and T. Bogri, Tetrahedron Lett., 1960, 17.
11. K. Wiesner and T. Inaba, J. Am. Chem. Soc., 91, 1036 (1969).
12. V. A. Tel'nov, M. S. Yunusov, and S. Yu. Yunusov, Khim. Prir. Soedin., 9, 129 (1973), English translation.
13. S. W. Pelletier, W. H. DeCamp, S. D. Lajšić, Z. Djarnati, A. H. Kapaldi, J. Am. Chem. Soc., 96, 7815 (1974).
14. S. W. Pelletier, Z. Djarnati, and S. Lajšić, J. Am. Chem. Soc., 96, 7817 (1974).
15. M. Przybylska, Can. J. Chem., 41, 2911 (1963).
16. R. Aneja and S. W. Pelletier, Tetrahedron Lett., 1964, 669.
17. R. Aneja and S. W. Pelletier, Tetrahedron Lett., 1965, 215.
18. S. W. Pelletier and R. Aneja, Tetrahedron Lett., 1967, 557.
19. R. Aneja, D. M. Locke, and S. W. Pelletier, Tetrahedron, 29, 3297 (1973).
20. (a) K. Wiesner, W. Kao, and J. Santroch, Can. J. Chem., 47, 2431 (1969); (b) K. Wiesner and J. Santroch, Tetrahedron Lett., 1966, 5939; (c) K. Wiesner, E. W. K. Jay, C. Demerson, T. Kanno, J. Krepinsky, L. Poon, T. Y. R. Tsai, A. Vilim, and C. S. Wu, Experientia, 26, 1030 (1970); (d) K. Wiesner, E. W. K. Jay, and L. Jay, Experientia, 27, 363 (1971).
21. J. P. Johnson and K. H. Overton, J. Chem. Soc., Perkin I, 1972, 1490.
22. K. Wiesner, R. Vlahov, and K. Muzika, Tetrahedron Lett., 1973, 2309.
23. K. Wiesner, T. Y. R. Tsai, K. Huber, and S. Bolton, Tetrahedron Lett., 1973, 1233.
24. K. Wiesner, T. Y. R. Tsai, K. Huber, S. E. Bolton, and R. Vlahov, J. Am. Chem. Soc., 96, 4990 (1974).
25. K. Wiesner, P. T. Ho, W. C. Liu, and M. N. Shanbhag, Can. J. Chem., 53, 2140 (1975).

INTRAMOLECULAR HYDROGEN BONDING

Reported by Barbara Mann

November 6, 1975

Hydrogen bonding occurs between a proton donor group A-H and a proton acceptor group B. This is generally represented as A-H...B, and can be either intermolecular or intramolecular. For intramolecular hydrogen bonding to occur, A and B must be able to assume a favorable spatial relationship within the molecule; that is, the distance between the hydrogen of A-H and B is between 1.4 and 2.5 Å, and B is "close" to the bond axis of A-H.¹ This seminar will look at intramolecular hydrogen bonding, presenting thermodynamic data when available and comparing IR frequency shifts and NMR chemical shifts with various molecular parameters. The importance of intramolecular hydrogen bonding to conformational analysis will be demonstrated with various diols. While many different proton donor groups participate in hydrogen bonding, much of the fundamental work which will be presented here has been done on O-H...B systems because these systems form strong hydrogen bonds. The comparisons developed here for simple molecules can provide guidelines for examining more complex systems. It was the known approximate geometries of the N-H...O hydrogen bonds that led to the first successful predictions of structure for proteins and DNA.²

For convenience hydrogen will be abbreviated as H in phrases such as hydrogen bond and hydrogen bonding for the rest of this seminar.

O-H...Halogen

o-Halophenols were among the first examples of intramolecular H bonding to be studied,³ however the nature of this bond is still in doubt. It is well established that o-halophenols exist as a mixture of two isomers, both in solution and the gas phase.⁴ These two isomers, the trans or free form and the cis or bonded form are shown in Figure 1. Two bands are found in the O-H stretching region in the IR. The higher frequency band is assigned to the trans isomer and the lower to the cis. The differences in frequencies for the two forms, $\Delta\nu = \nu_s(\text{trans}) - \nu_s(\text{cis})$, are found to increase with the size of the halogen atom, as does the percentage of trans isomer. If ΔH increases proportionally to $\Delta\nu$, a relationship which is true for many intermolecular H bonds,^{2,5} then the iodine atom should form the strongest H bond and fluorine the weakest. Table I summarizes the values calculated for ΔH for o-halophenols using different methods, showing this is not the case. There is general agreement in the relative order of intramolecular H bond strength of $\text{Cl} > \text{Br} > \text{I}$, both in solution and in the gas phase, but the position of fluorine is disputed. The most reliable figures for ordering the H bond strengths are those obtained by torsional frequency measurements, ν_σ , in the IR since they do not involve intensity measurements. If one accepts these values the general ordering for intramolecular H bond strengths is $\text{Cl} > \text{Br} > \text{I} > \text{F}$ in solution and $\text{F} = \text{Cl} > \text{Br} > \text{I}$ in the gas phase.⁶ The order of H bond strengths found in the gas phase is that expected if size and electronegativity are of prime importance. On this basis fluorine should form the strongest H bond. Perhaps due to the small size of the fluorine atom the H...F distance is too long to form as strong a H bond as predicted. The apparent stabilization of the trans isomer of o-fluorophenol in solution is attributed to the formation of dimers.

Figure 1.

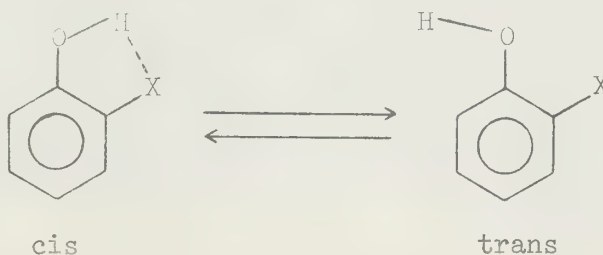


Table I. Enthalpies Calculated by Different Methods for the O-H...X Intramolecular H Bond in o-Halophenols.

X	IR		$\Delta\nu_{\text{O}}$	ν_{O} d area	$-\Delta H$ kcal/mole			NMR ^c (CS ₂)	NMR ^{a,b} (CCl ₄)
	ν_{S}	(CCl ₄)			ν_{O} d peak height	ν_{O} e (gas)	ν_{O} e (CCl ₄)		
F	-	3591.0	-	1.19	-	1.63	1.44	-	1.53
Cl	3603.2	3547.1	61	1.44	1.63	1.63	1.62	2.36	1.91
Br	3602.7	3527.8	78	1.21	1.62	1.53	1.57	2.14	1.91
I	3600.0	3505.1	105	1.08	1.44	1.32	1.45	1.65	1.45

^aThis study gives relative ΔH values. ΔH -1.45 for X = I is taken as the reference point. ^bReference 36. ^cReference 37. ^dReference 9. ^eReference 6.

NMR studies reveal the presence of a strong intramolecular H bond for o-trifluoromethylphenol.⁷ With the formation of a six-membered H-bonded ring, compared to the five-membered ring formed in o-fluorophenol, the small size of the fluorine atom is no longer important in determining the H...F distance. The strong H bond predicted on the basis of fluorine's high electronegativity is found.

Solvent effects on the cis-trans equilibrium of o-iodophenol have been investigated.⁸ The data in Table II indicate that as the H bonding ability of the solvent increases, the stability of the trans isomer increases. The polar solvents break intramolecular H bonds and replace them with H bonds to the solvent. This also indicates that the data obtained in different solvents must be compared with caution.

Table II. Enthalpies of the Intramolecular H Bond Formed in o-Iodophenol in Different Solvents.

Solvent	ν_{S} (cm ⁻¹)	$-\Delta H$ kcal/mole
CH ₂ Br ₂	-	3489.2
CHCl ₃	3584.6	3500.7
CCl ₄	3600.0	3505.1
iso-C ₈ H ₁₈	3612.4	3509.5
C ₁₀ H ₁₈	3637.6	3517.6

Enthalpies calculated from measurements of peak heights of hydroxyl stretching frequencies for 2-haloethanols give the order of H bond strengths F > Br ≥ Cl > I.⁹ The data for 2-fluoroethanol are highly suspect. Solution studies and a recent electron diffraction study¹⁰ indicate that this compound exists in the gauche conformation in the gas phase (>95%) and in solution (CCl₄).¹¹ This has been interpreted as evidence for the existence of a strong intramolecular H bond. Recent NMR studies suggest a very weak, if any, intramolecular H bond exists.¹¹ The OH proton is found to behave much like the OH proton of ethanol in variable concentration and temperature studies.

Torsional frequencies in the IR, $\nu_{\text{C}}^{\text{O}}$, were also used to calculate $-\Delta H$ for a number of other *o*-substituted phenols; for *o*-methoxy, 2.0, *o*-ethoxy, 2.31, *o*-cyano, 1.73, and *o*-phenyl, 2.73.¹² All of these form stronger intramolecular H bonds than the *o*-halophenols.

O-H...O=C

Lineshape analysis of pmr singals has been used to calculate the effect of intramolecular H bonds on the rotational barrier in 2,6-diformylphenols.¹³ As illustrated in Figure 2, rotation around the C(aryl)-C(formyl) bond causes the environments of H_1 and H_2 , and H_X and H_Y to interchange. Variable temperature spectra were measured in CDCl_3 and the rotational barrier heights were determined to be 11.0 kcal/mole for the *p*-Cl and *p*-CH₃ derivatives. The difference of 3.5 kcal/mole between this value and the rotational barrier in benzaldehyde is attributed to the intramolecular H bond energy. This value is somewhat low considering the high stability of the intramolecularly H bonded forms of other *o*-hydroxyphenyl carbonyl compounds indicated by IR and NMR studies. In another pmr study, where diethyl ether was the solvent, very little difference in rotational barrier heights compared to benzaldehyde was found.¹⁴ This was explained by the authors by the scheme shown in Figure 3, where due to solvent participation or dimerization, a major fraction of the H bond enthalpy is conserved during the reaction. The rupture of the intramolecular H bond may occur together with or after complex formation.

One of the few direct rate studies on intramolecular H bonding was done on methyl and ethyl salicylate and salicylaldehyde using ultrasonic absorption techniques.¹⁵ Rate constants for the dissociation reaction shown in Figure 4 were calculated at several temperatures. The difference between the energies of activation for the forward and reverse reactions, ΔE , is a measure of the strength of the intramolecular H bond. This value of 3.4 kcal/mole is comparable to the value of 3.5 kcal/mole obtained from the pmr study discussed previously.

Figure 2

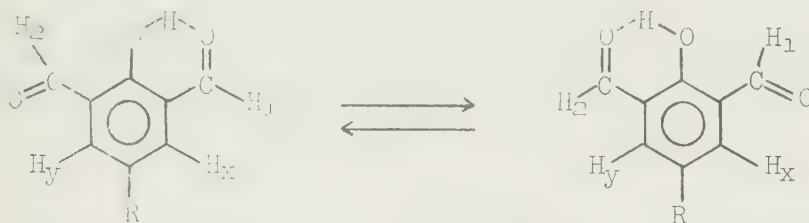


Figure 3

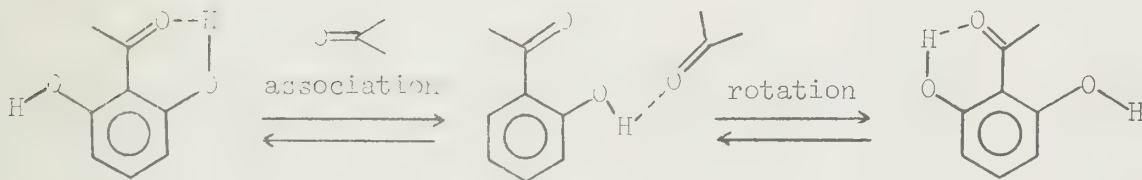


Figure 4



Keto-enol tautomerism in β -dicarbonyl compounds has been studied using NMR. NMR provides a convenient method for studying this system because the keto and enol isomer each generally gives rise to a separate set of peaks. Higher temperatures and polar solvents favor the keto isomer.¹⁶ Thermodynamic data have been obtained for the tautomerization, however, the error is large because ΔH and ΔS are temperature dependent.¹⁶ The thermodynamic data available imply that the enol form is in general more stable, but because of the large entropy of enolization, the keto form is present in substantial amounts and may even predominate at equilibrium.

O-H...O-C

Intramolecular H bonding in 1,2-, 1,3-, and 1,3-diols has been investigated by several workers. Studies of 1,2-diols indicate the differences between hydroxyl stretching frequencies of the bonded and nonbonded forms, $\Delta\nu_s$, are proportional to changes in the O...H distance.¹⁷ A shorter O...H distance results in a stronger H bond and a larger $\Delta\nu_s$. The azimuthal angle, ϕ , defined as the angle between two C-O bonds on adjacent carbon atoms when looking down the C-C bond, is of prime importance in determining the O...H distance. Table III illustrates the relationship of the azimuthal angle to $\Delta\nu_s$. For 1,2-diols, as ϕ decreases, the H...O distance decreases, and $\Delta\nu_s$ increases.¹⁷ Most cyclic 1,2-diols have azimuthal angles near 60° and $\Delta\nu_s$ ranging from 30 to 50 cm^{-1} .

In acyclic substituted ethylene glycols, nonbonded repulsions between R groups results in larger $\Delta\nu_s$ for dl and threo isomers than for meso and erythro isomers.¹⁸ In the dl and threo isomers, these repulsions force the hydroxyls closer together resulting in a shorter H...O distance. The same repulsions in the meso and erythro isomers force the hydroxyls apart, as shown with the Newman projections in Figure 5. Bulky substituents on ethyleneglycol also cause $\Delta\nu_s$ to increase, because steric crowding forces the hydroxyls closer together.¹⁸ Also, 1,3-diols behave quite similarly to 1,2-diols.

Table III. The Relationship between $\Delta\nu_s$, ϕ , and H...O Distance.

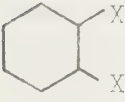
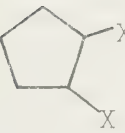
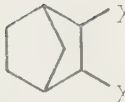

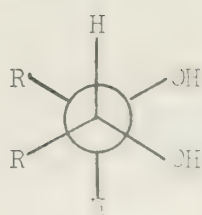
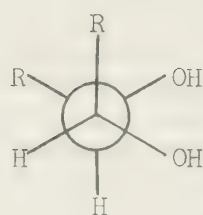
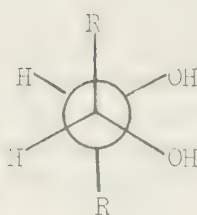
Compound	Configuration	ϕ	1,2-diols X = OH $\Delta\nu_s$	1,4-diols X = CH_2OH $\Delta\nu_s$	H...O Distance A
	cis	60	38	136	2.34
	trans				
	equatorial	60	33	144	2.34
	axial	180	-		
	cis	0	61	131	1.84
	trans	120	0	159	3.3
	cis	0	61	133	
	trans	125	0	136	
	trans	120	-	155	

Figure 5



dl or threo

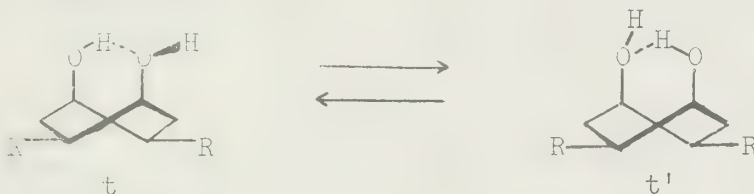


meso or erythro

The spectral behavior of 1,4-diols appears quite different from the analogous 1,2-diols. While $\Delta\nu_s$ in 1,2-diols shows a smooth increase as ϕ decreases, 1,4-diols exhibit a maximum $\Delta\nu_s$ when $\phi = 90^\circ$ and no other apparent regularity.¹⁸ When $\phi = 0^\circ$, the O-H...O angle is 180° , permitting the shortest O...H distance possible, and the C-O...H angle is 110° , suggesting overlap of an oxygen lone pair with H. When ϕ is less than 90° molecular models show that more than one conformation is possible in which intramolecular H bonding can occur. Many 1,4-diols do show multiple bonded peaks in the IR.

Plots of $\log k$ vs. $1/T$ give enthalpy values for the intramolecular H bonds in diols. In general, the strength of the H bonds are 1,4-diol > 1,3-diol > 1,2-diol = 2,3-diol.¹⁹ Also the magnitude of ΔH for each diol is greater in the vapor phase than in solution. A linear relationship exists between Δv_s and ΔH for all intramolecularly H bonded butanediols.

Studies of cyclohexanediols have utilized the relationship of the azimuthal angle to $\Delta\nu_s$ to determine preferred conformers.²⁰ If H bonding occurs in a trans-1,2-cyclohexanediol, the hydroxyl groups must be equatorial, and in a cis-1,3-diol, they must be axial. For 1,2-cyclopentanediols intramolecular H bonding can occur only if one hydroxyl is axial and the other equatorial. Intramolecular H bonding can occur in 1,4-cyclohexane diols if the hydroxyl groups are cis and the molecule can achieve a twist conformation.²¹ The twist conformer population increases with the sizes of cis-2,5-dialkyl substituents. The doublet of free hydroxyl absorptions found in the t-alkyl substituted compounds is interpreted in terms of two nonequivalent twist conformations, t and t', present in nearly equal populations.



Thermodynamic and conformational data have been obtained for 2-methoxyethanol, 3-methoxyethanol, and 4-methoxyethanol, and compared to the data on the intermolecular H bond between butanol and diethyl ether.²² A linear relationship between Δv and ΔH was observed for the intermolecular bond and for 3-methoxyethanol. If the interaction between donor and acceptor in the formation of the H bond, as measured by Δv_s , is the principal interaction in forming the H bond then Δv_s will be linearly related to ΔH . This is generally assumed to be the case for intermolecular H bonds.²³ On the other hand, if conformational changes are major in forming the H bond, then ΔH will be the sum of all interactions and will not be so simply related to Δv_s . The difference between the predicted ΔH (using the Joesten-Drago equation)²⁴ and the experimental ΔH can be interpreted as a measure of the repulsive interactions lost or gained due to conformational changes.²²

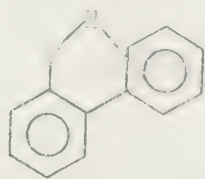
IR spectroscopy has been applied to a conformational study of cyclopentane- and cyclohexane-1,2-diol monoacetates.²⁵ H bonding is observed to both the carbonyl and alkoxyl oxygens. The H bond to the alkoxyl oxygen is weak, causing only a small shift relative to the free hydroxyl. In trans-cyclopentane and trans-cyclohexane-1,2-diol monoacetates both free and carbonyl bonded hydroxyls are observed. Intramolecular H bonding is possible only in the equatorial conformation. cis-Cyclopentane-1,2-diol monoacetate shows two different H bonded hydroxyl peaks and no free peaks. The same situation is observed for the cis-cyclohexane compound.

IR and electron diffraction studies reveal that gaseous ethylene glycol monoformate exists in two gauche conformers, both of which have intramolecular H bonding.²⁶ In one conformer the H bond is directed toward the ester oxygen, and in the other toward the carbonyl oxygen. Two carbonyl absorptions at $\nu_s = 1720$ and 1755 cm^{-1} are seen in the IR spectrum. Electron diffraction results give H bond lengths of 2.78 and 2.81 Å.

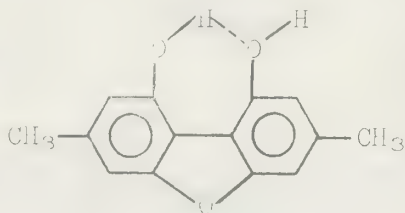
O-H...C=C

The pi electron systems of olefins, acetylenes and aromatic compounds can function as proton acceptor sites in H bonding. 2-Hydroxyl biphenyl(I) has two hydroxyl stretching frequencies at 3605 and 3565 cm^{-1} , which are assigned to the free hydroxyl and the hydroxyl H bonded to the phenyl ring respectively.²⁷ Compound II shows two peaks which are attributed to the free OH and a strong O-H...O bond. This molecule is nearly planar, preventing the orbital overlap necessary to form O-H... π bonds. Compound III has a free OH peak, a peak due to an O-H... π bond, and no O-H...O peak. Here the phenyl rings are nearly perpendicular. Intramolecular H bonds can occur as long as the OH and the pi system are not coplanar. Equations have been developed for predicting ν_s (bonded) based on the angle between the plane of the benzene ring and the plane containing the α and β carbons.²⁸

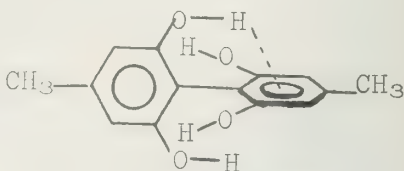
The $-\Delta H$ of this interaction has been calculated using peak height measurements of ν_s to be approximately 1 kcal/mole.²⁷ Calculations based on torsional frequencies measurements give $-\Delta H$ 2.73 kcal/mole.¹² Torsional frequency calculations give the inherent strength of the H bond, while measurements taken from equilibrium measurements give a H bond strength which has been affected by entropy. With the assumption of $-\Delta H$ of 2.73 kcal/mole and an entropy decrease of 3 to 4 e.u. upon H bond formation, the correct equilibrium position is obtained.¹²



I



II



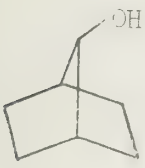
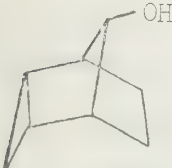


III

Evidence for intramolecular OH... π bonding is also found in the spectra of benzyl and allyl alcohol.²⁹ In benzyl alcohol, OH stretching peaks are found at 3636.3 and 3617.1 cm^{-1} , and in allyl alcohol at 3634.8 and 3619.4 cm^{-1} . This seems to imply there is little difference between conjugated and isolated pi systems when acting as proton acceptors. The microwave spectrum of allyl alcohol indicates the primary conformer in the vapor phase is the gauche conformer which permits H bonding.³⁰

Intramolecular O-H... π bonds have been observed for hydroxyl acetylenes and nitriles.³¹ The H bond in the nitriles is formed to the π system of $C\equiv N$, not to the nitrogen atom. If the hydroxyl is located α or β to the nitrile intramolecular H bonding is observed. No intramolecular H bonding of any kind is observed if the hydroxyl is further removed. For the analogous acetylene compounds intramolecular H bonds are seen for α , β , and γ hydroxyls. From this it may be concluded that a carbon-carbon triple bond is a better proton acceptor than the carbon-nitrogen triple bond.

Cyclopropane rings may serve as proton acceptors in H bonding.³² Careful interpretation of the spectra is necessary since many saturated alcohols with no proton acceptor sites give comparable spectra due to conformational heterogeneity.³³ While there is no evidence for H bonding in cyclopropylethanol itself, more rigid, properly oriented compounds give well-defined two-peak spectra. A variety of compounds are listed in Table IV which indicate this interaction, as well as the necessary geometry. The cyclopropane ring is a weaker proton acceptor than a double bond. Intramolecular H bonding has been demonstrated when the hydroxyl is α or β to a cyclopropane ring.

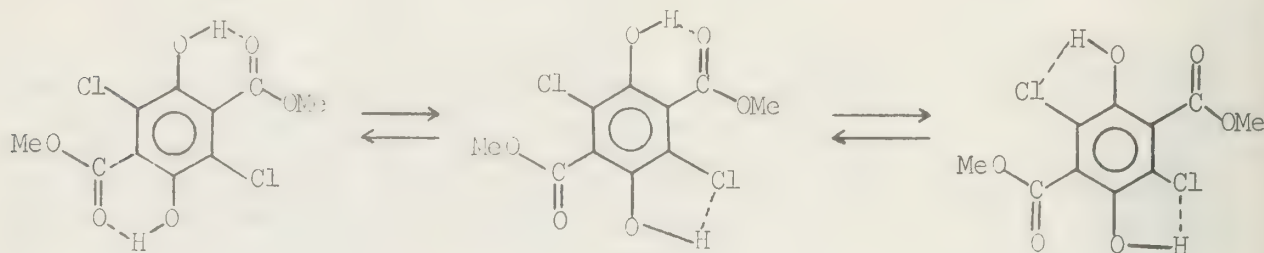
Table IV. Spectral Measurements for Cyclopropyl Alcohols

Compound	ν_s	$\Delta\nu$
	3630	-
	3632	-
	3631 3596	35
	3630	-

One last example of intramolecular H bonding will be taken from the solid state. In solution, dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate exists as a solvent-dependent mixture of three isomers, shown in Figure 7, determined from IR and UV solution studies and nuclear quadrupole resonance measurements.³⁴ Two different crystalline forms exist which, after X-ray structure determination, are found to differ in a manner reminiscent of the isomers in solution. The

yellow form has an intramolecular H bond between the phenolic hydroxyl and the carbonyl oxygen, and the white form has a bifurcated H bond from the phenolic hydroxyl to the chlorine atom and to the carbonyl oxygen in the next molecule. Stereoisomerism about a carbon oxygen single bond due to the presence of different H bonding schemes is the major difference between the two forms of this compound.

Figure 7.



Vast amounts of information on intramolecular H bonding are available today. Many different spectroscopic techniques can be used to study H bonding, the most important being IR and NMR. Although not discussed here, studies of H bonds in the solid state have proven very important. Here very accurate analysis of the geometry of the H bond is possible. Correlations between various molecular parameters and spectroscopic measurements have been attempted and have had limited success. However much work still needs to be done. For instance, the best geometrical arrangement for H bonding is not known. Is the linear H bond the strongest as implied by the data gathered for intermolecular H bonds? Or is the A-H...B angle of only minor importance as suggested by the wide range of values found in intramolecular H bonding?² Continuing investigation in this field will bring better understanding of the factors which control the geometry and strength of the H bond.

BIBLIOGRAPHY

1. S. N. Vinogradov, R. H. Linnell, "Hydrogen Bonding," Van Nostrand Reinhold Company, 1971.
2. W. C. Hamilton, J. A. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, Inc., 1968.
3. D. R. Wulf, U. Liddel, S. B. Hendricks, J. Am. Chem. Soc., 58, 2287 (1936).
4. G. C. Pimental, A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Company, 1960.
5. G. C. Pimental, C. H. Sederholm, J. Chem. Phys., 24, 639 (1956).
6. G. L. Carlson, W. G. Fately, A. S. Manocha, F. F. Bentley, J. Phys. Chem., 76, 1553 (1972).
7. D. Doddrell, E. Wenkert, P. V. Demarco, J. Mol. Spec., 32, 162 (1969); A. W. Baker, A. T. Shulgin, Nature, 206, 712 (1965).
8. A. W. Baker, A. T. Shulgin, Spectrochim. Acta, 22, 95 (1966).
9. A. W. Baker, A. T. Shulgin, Can. J. Chem., 43, 650 (1965).
10. K. Hagen, K. Hedberg, J. Am. Chem. Soc., 95, 8263 (1973).
11. R. C. Griffiths, J. D. Roberts, Tetrahedron Lett., 39, 3499 (1974).
12. G. L. Carlson, W. G. Fately, J. Phys. Chem., 77, 1157 (1973).
13. M. Tabei, T. Tezuka, M. Hirota, Tetrahedron, 27, 301 (1971).
14. U. Koelle, S. Forsen, Acta. Chemica Scand., 28A, 531 (1974).
15. T. Yasunaga, N. Tatsumoto, H. Inoue, M. Muira, J. Phys. Chem., 73 447 (1969).
16. J. L. Burdett, M. T. Rodgers. J. Phys. Chem., 70, 939 (1966).

17. L. P. Kuhn, J. Am. Chem. Soc., 74, 4422 (1952).
18. L. P. Kuhn, P. Schleyer, W. F. Baitinger, L. Ebersson, J. Am. Chem. Soc., 86, 650 (1964).
19. E. Fishman, T. L. Chen, Spectrochim. Acta., 25A, 1231 (1969).
20. M. D. Joesten, L. J. Schaad, "Hydrogen Bonding," Marcel Dekker, Inc., 1974.
21. R. D. Stelow, P. M. McDonagh, M. M. Bonaventura, J. Am. Chem. Soc., 86, 2165 (1964).
22. L. P. Kuhn, R. A. Wires, J. Am. Chem. Soc., 86, 2161 (1964).
23. L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co., LTD, 1968.
24. M. D. Joesten, R. S. Drago, J. Am. Chem. Soc., 84, 3817 (1962).
25. R. W. Wright, R. H. Marchessault, Can. J. Chem., 46, 2569 (1968).
26. J. Bijen, J. Mol. Struct., 17, 69 (1973).
27. M. Oki, H. Iwamura, J. Am. Chem. Soc., 89, 576 (1967).
28. H. Iwamura, Tetrahedron Lett. 2227 (1970).
29. M. Oki, H. Iwamura, Bull. Chem. Soc. Japan, 32, 567 (1959); 32, 955 (1959).
30. A. Murty, R. F. Curl, Jr., J. Chem. Phys., 46, 4176 (1967).
31. A. Allerhand, P. Schleyer, J. Am. Chem. Soc., 85, 866 (1963).
32. L. Joris, P. Schleyer, R. Gleiter, J. Am. Chem. Soc., 90, 327 (1968).
33. L. Joris, P. Schleyer, E. Osawa, Tetrahedron, 24, 4759 (1968).
34. D. Y. Curtin, S. R. Byrn, J. Am. Chem. Soc., 91, 6102 (1969).
35. S. R. Byrn, D. Y. Curtin, I. C. Paul, J. Am. Chem. Soc., 94, 890 (1972).
36. J. B. Rowbotham, T. Schaefer, Can. J. Chem., 52, 3037 (1974).
37. E. A. Allan, J. G. Reeves, J. Phys. Chem., 66, 613 (1962); 67, 591 (1963).

STRUCTURE DETERMINATION OF EVERNINOMICIN D

Reported by Yang M. Goo

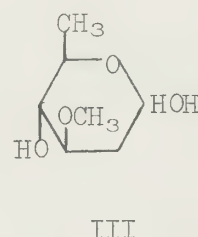
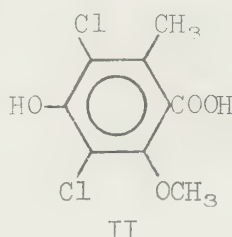
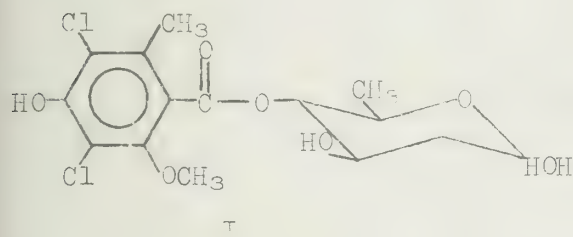
November 10, 1975

Since the isolation of the antibiotic exfoliatin by Umezawa¹ in 1952, a number of structurally related antibiotics including curamycin (1961),² avilamycin (1962),³ everninomicin (1964)⁴ and flambamycin (1974)⁵ have been isolated from cultures of *Streptomyces* or *Micromonospora*. These members have very similar characteristics; all exhibit positive Molish test, they yield curacin (I) as a hydrolysis product and they are chiefly active against gram positive organisms. These novel oligosaccharide antibiotics are generally classified as everninomycins. The name comes from the fact that a derivative of everninic acid (II) is an important constituent of this class of antibiotics. Until recently the structures of this series of antibiotics have been unknown. The first successful structure determination has been accomplished for everninomicin D by Ganguly and coworkers.⁶ The present report discusses the complete structure determination of everninomicin D and treats firstly the general structural characteristics, secondarily the identification of subunits obtained by hydrolysis and thirdly recombination of these subunits to provide the total structure of everninomicin D.

Everninomicin D is a major constituent of the everninomicin antibiotic complex⁷ produced by a species of *Micromonospora*⁸ which was isolated from a soil sample obtained in Olean, N. Y. by Weinstein et. al.⁹ Elemental analyses of everninomicin D showed the presence of C, H, Cl, N and O. Its uv spectrum displays a maximum absorption at 289 nm. in methanol solution which shifts to 295 nm. in 0.1 N. methanolic sodium hydroxide solution with a three fold enhancement of intensity. Its ir spectrum is rich in detail with intense absorption around 3333 cm^{-1} (hydroxyl groups), 1730 cm^{-1} (carbonyl group), 1538 cm^{-1} (nitro group) 1250 cm^{-1} (ester group) and 1110 cm^{-1} (ether groups).¹⁰ Titration of everninomicin D with sodium hydroxide in methanol solution gives an equivalent weight of approximately 1500.^{10,11} Everninomicin D on hydrolysis with aqueous acid yields a mixture of products from which the following compounds have been isolated and characterized.

Everninocin¹²

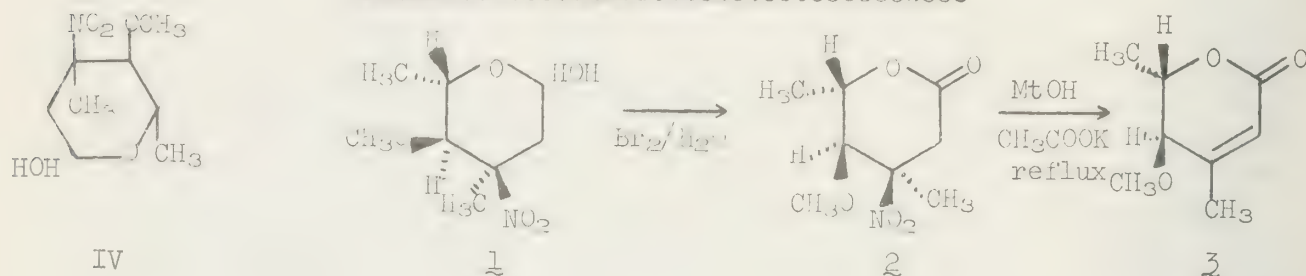
The structure of everninocin has been found to be identical to that of curacin (I) which can be obtained from hydrolysis products of curamycin¹³ or avilamycin.¹⁴ Vigorous hydrolysis of everninocin gives two products, dichloro-isoverninic acid (II) and 2,6-dideoxy-D-arabinose (III).

Evernitrore¹⁵

Evernitrore, $\text{C}_8\text{H}_{15}\text{NO}_5$, shows mutarotation and has bands assigned to a nitro group (1553 cm^{-1}) and a hydroxyl group in its ir spectrum. Acetylation affords a monoacetate which exhibits a secondary methyl group (δ 1.38, d, $J=7\text{Hz}$), a tertiary methyl group (δ 1.71, s), an acetate methyl group (δ 1.95, s), a methoxy group (δ 3.88, s), a one proton multiplets (δ 3.55), a one proton doublet (δ 3.38, $J=6\text{Hz}$) and one axial anomeric proton (δ 5.80, q, $J=8\text{Hz}$ and 3Hz) in its pmr spectrum. The presence of the nitro group in evernitrore is also indicated by an M-NO_2 (m/e 159) peak in its mass spectrum. From these data, structure IV has been deduced for evernitrore. To confirm this structure, evernitrore was

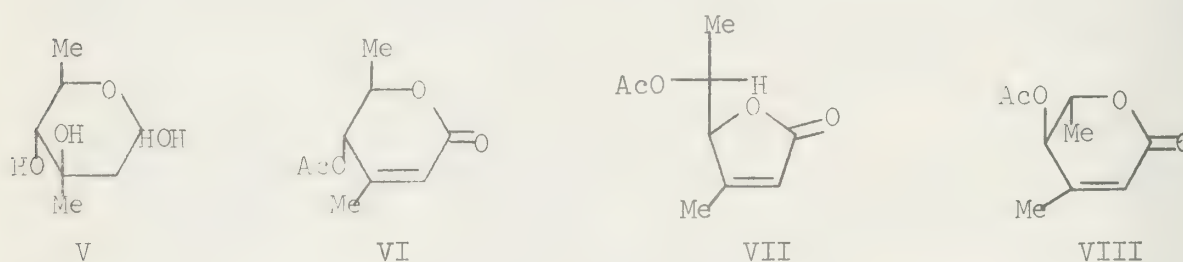
methylated then catalytic hydrogenated to afford a compound which had an amine group. Acetylation of the amine gave a compound which had an N-acetyl methyl resonance at δ 1.95 in its pmr spectrum. This suggests axial configuration of the acetamide group. (It has been predicted that the expected range of axial acetamide group on carbon bearing methyl would be δ 1.95 - 1.86 compared to δ 1.87 - 1.78 for their equatorial counterpart¹⁶). Modification of evernitrose as shown in Figure 1 was carried out to confirm its absolute stereochemistry. The final product (3) was found to be identical to that obtained from similarly modified mycarose.

Figure 1. Modification of evernitrose



Evermicosose¹⁸

Evermicosose, $C_7H_{14}O_4$, has no absorption in its uv spectrum above 210 nm and no carbonyl absorption in its ir spectrum. Evermicosose forms a diacetate ($C_{11}H_{18}O_6$) which shows peaks in its pmr spectrum at δ 1.2 (d, CH_3 , $J=6Hz$), 1.3 (s, CH_3), 2.1 and 2.13 ($2COCH_3$), 4.6 (d, 1H, $J=10Hz$) (octet, 1H, $J=10Hz$ and 6Hz), 5.75 (q, 1H, $J_{aa}=9Hz$, $J_{ae}=3Hz$) and 2.6 (OH). From these data evermicosose was inferred to be 3-epimycarose (V).¹⁹ To prove the suggested structure evermicosose was oxidized with bromine to the lactone which was directly acetylated and dehydrated in benzene containing a catalytic amount of TsOH to afford compounds VI and VII. Compound VIII was synthesized from L-mycarose¹⁷ and it was identical to VI except that it had $[\alpha]^D_{-99.8}$. (cf. $[\alpha]^D_{+97.8}$ for VI).

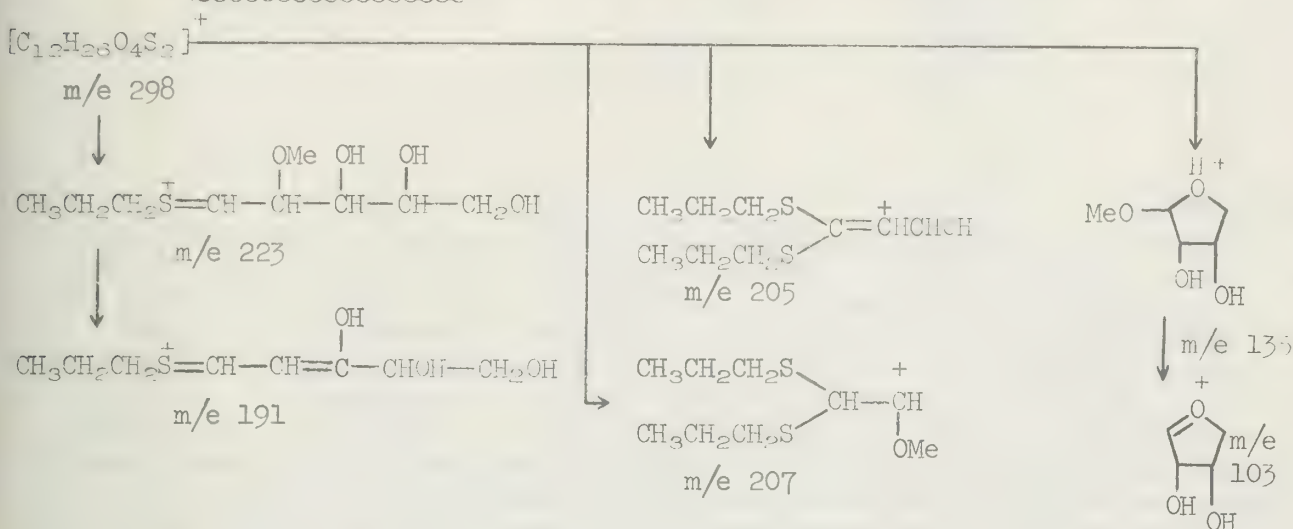


Everninose²⁰

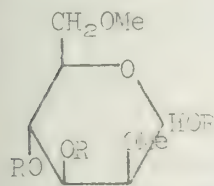
The aniline-phthalate²¹ positive fraction of column chromatography of the everninomicin D hydrolyzate was named everninose. It is a non-reducing sugar which consumes two moles of periodate but does not form a trityl²² derivative. The pmr spectrum of everninose shows the presence of three methoxy groups and two anomeric protons. Everninose, $C_{14}H_{26}O_{10}$ formed a tetraacetate ($C_{22}H_{34}O_{14}$). The mass spectrum of the tetra-O-trimethylsilyl ether of everninose shows a strong M-15 peak at m/e 627 besides a small molecular ion peak at m/e 642. Other prominent peaks are at m/e 335 and m/e 291 which indicate that everninose is composed of

dimethoxy hexose and a monomethoxy pentose which are linked through their anomeric hydroxy groups. Upon prolonged heating with aqueous acid everninose was hydrolyzed into a mixture of two monosaccharides which were separated by preparative tlc. One compound formed a triacetate which was identical to triacetoxycuramicose (IX). By permethylation of everninose followed by hydrolysis, this hexose unit was identical to 2,3,4,6-tetra-O-methyl-D-mannose. From this information structure X was assigned for the dimethoxy hexose unit. The other pentose part ($C_5H_9O_5$) formed a di-n-propyl mercaptal ($C_{12}H_{26}O_4S_2$) whose mass spectrum shows ions at m/e 298, 223, 207, 205, 191, 135 and 103 which can be assigned as shown in Figure 2. This mass spectrum confirmed that the compound was a 2-methoxy pentose.

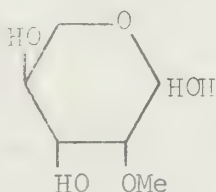
Figure 2. Assignments of major ions in the mass spectrum of di-n-propyl mercaptal pentose.



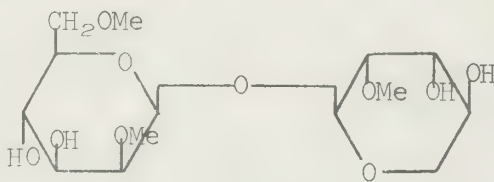
Permethylation of the 2-methoxy pentose followed hydrolysis afforded a compound which was identical to an authentic sample of 2,3,4,-trimethoxy-D-lyxose²³ except that it had the opposite sign of rotation. Structure XI was assigned for the 2-methoxy pentose. On methylation everninose yielded a compound which has $[M]_D = -356$. By applying Klyne's rule²⁴ β -glycoside bond was determined. Structure XII was assigned to everninose.



R = OAc IX
R = H X



XI

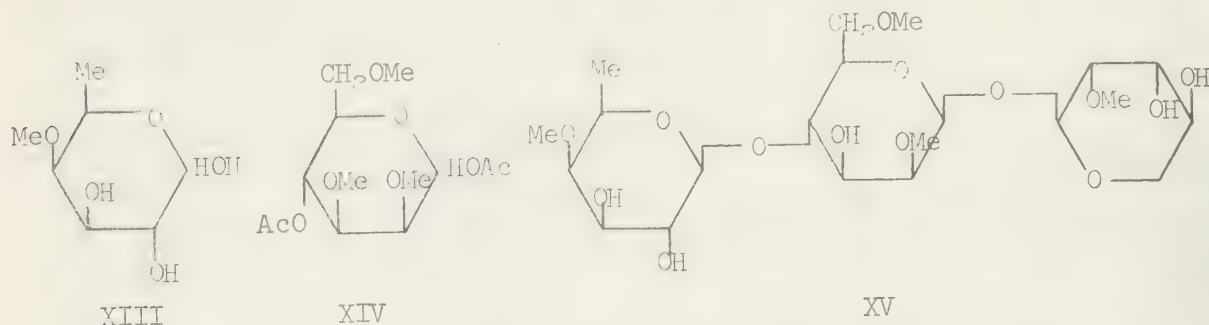


XII

Evertriose²⁵

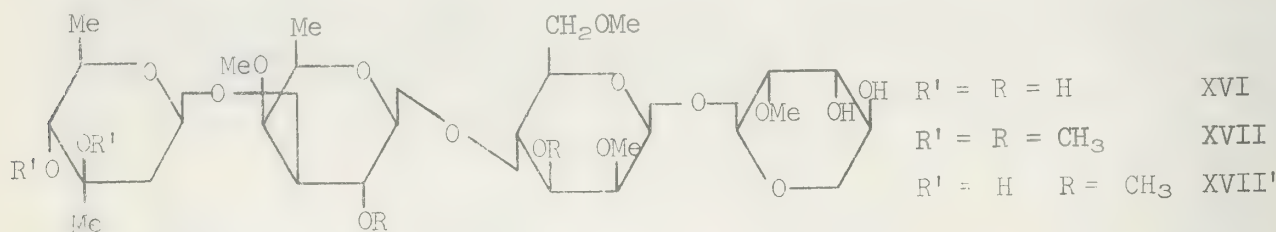
The isolated tri-saccharide, evertriose ($C_{21}H_{38}O_{14}H_2O$) is a nonreducing sugar and does not have selective absorptions in its uv or ir spectra. Further hydrolysis of evertriose yielded everninose (XIII) and D-curacose (XIII)²⁶ which were identified by comparison of their tosylhydrazone with those of authentic sample. The pmr spectrum of permethylated evertriose shows three anomeric protons. One anomeric proton shows resonances at δ 4.36 (d, $J=7$ Hz) and it is attri-

buted to that of the curacose. The other two belongs to the everninose portion. From this pmr coupling constant data β -anomeric linkage was established. The stereochemistry of the anomeric linkage of curacose was further confirmed by the application of Klyne's rule.²⁴ Prolonged hydrolysis of permethylated evertriose yielded a mixture from which one component was isolated and proved by acetylation to have structure XIV. The isolation of this compound indicates that in evertriose D-curacose is linked to the C-4 of hexose moiety of everninose. These facts establish the structure and stereochemistry of evertriose (XV).



Evertetrose²⁷

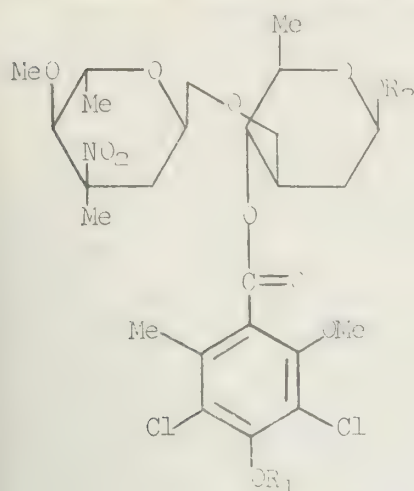
Evertetrose, a non-reducing sugar, shows no distinctive uv absorption and no carbonyl's absorption in its ir spectrum. Hydrolysis with aqueous acid yielded evertetrose (XV) and evermicosose (V). Methylation afforded the permethylated compound which on prolonged hydrolysis gave a mixture of compounds: more polar component was isolated and acetylated to give 2,4-dimethoxy-1,3-diacetoxy-D-curacose. Isolation of this compound establishes that evermicosose is linked to C-3 of curacose. The anomeric proton of evermicosose appears in the pmr spectrum of evertetrose at δ 4.85 (1H, q, $J=7$ Hz and 2Hz) whose coupling constants indicate α -linkage between C-1 of evermicosose and C-3 of curacose in evertetrose. The absolute stereochemistry was also determined by application of Klyne's rule.²⁴ Based upon these considerations structure XVI was assigned for evertetrose.



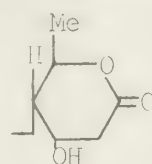
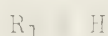
Everheptose²⁸

Everheptose, $C_{57}H_{89}Cl_2NO_{31}$, exhibits a nitro group (1538 cm^{-1}) and carbonyl groups (1730 cm^{-1}). A methanolic solution of everheptose when treated with ethereal diazomethane underwent smooth cleavage to yield a mixture of two compounds. The more polar one was shown to be identical to evertetrose (XVI). The less polar component (XXI), when stirred with silica gel in acetone changed to another stable compound ($C_{30}H_{41}Cl_2NO_{14}$). This stable compound has in its uv spectrum bands at 287 nm (ϵ 973) and 210 nm (ϵ 30159) and in its ir spectrum absorption at 1754, 1538 and 3472 cm^{-1} . It formed a monoacetate compound which showed no absorption of hydroxyl group in its ir spectrum. This monoacetate exhibits resonances in its pmr spectrum at δ 1.46 (d, $J=6.5$ Hz, CH_3), 2.67 and 2.95 ($J_{gem}=16$ Hz, CH_2), 3.65 (q, $J=8$ Hz and 3Hz, H of C-4), 4.25 (octet, $J=6.5$ Hz and 8Hz, H of C-5) and 5.49 (d of t, $J=4.8$ Hz and 3Hz) in addition to an acetate methyl absorption and the characteristic absorption of everninonitrose (XVIII).²⁷ From the pmr spectral data, the structure of this compound was given as XX. The relative stereochemistry at

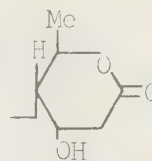
C-3, C-4 and C-5 of R₂ followed from the above coupling constants. Compound XXI can be regenerated from XX by TMSH and should have the structure shown (XXI).



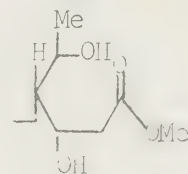
XVIII



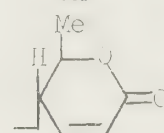
XIX



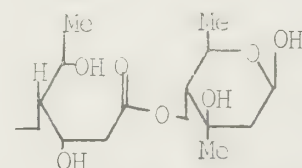
XX



XXI



XXII

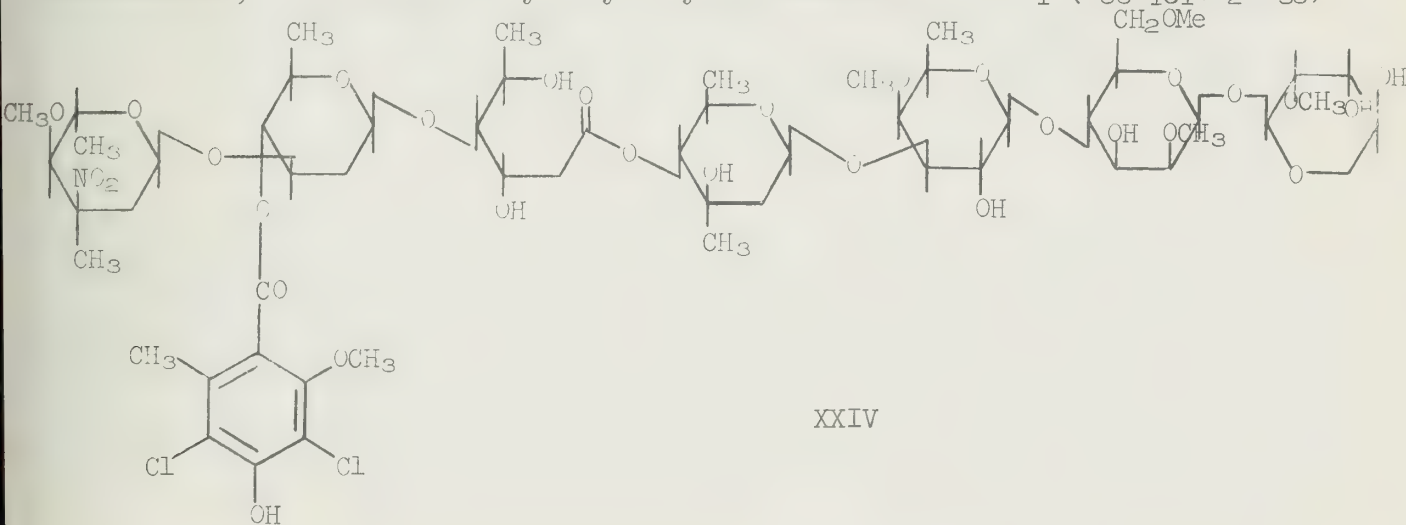


XXIII

Compound XX on heating with acetic anhydride and pyridine yielded an anhydrocompound ($\text{C}_{30}\text{H}_{39}\text{Cl}_2\text{NO}_{15}$) (XXII). The circular dichroism spectrum of compound XXII shows negative cotton effect $([\theta])_{250} = -40900$ suggesting the R-configuration at C-5 of R₂. The linkage of XIX to XVI in everheptose was achieved by deducing the structure of another hydrolysis product (XXIII). This compound (XXIII) ($\text{C}_{44}\text{H}_{61}\text{Cl}_2\text{NO}_{22}$), when treated with diazomethane underwent smooth cleavage to XXI and evermicose (V). They are connected between C-4 of evermicose and the carbonyl group of XXI by an ester bond, forming compound XXIII. From these facts the total structure (XXIV) of everheptose was assigned.

Total Structure of Everninocicin D⁶

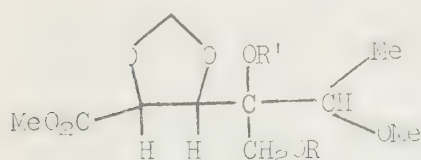
Everninomicin D, $\text{C}_{66}\text{H}_{99}\text{Cl}_2\text{NO}_{35}$, which forms a mono methyl ether with diazomethane, on mild acidic hydrolysis yields everninomicin D₁ ($\text{C}_{66}\text{H}_{101}\text{Cl}_2\text{NO}_{36}$).



XXIV

Treatment of everninomicin D₁ with diazomethane afforded smooth cleavage to XX and oligose. Oligose, C₇H₁₂O₅, does not show any carbonyl absorption in its ir spectrum. On solvolysis oligose yielded evertetrose (XVI) and an ester (C₁₀H₁₈O₇) (XXV) which showed in its ir spectrum absorptions at 1739 cm⁻¹ and 3509 cm⁻¹ and in its pmr spectrum resonances at δ 1.25 (d, 3H, J=6.5Hz, CH₃), 3.35 (s, -OCH₃), 3.81 (s, -COOCH₃), 3.6 - 3.9 (multiplet, 3H), 4.19 (d, 1H, J=5Hz), 4.85 (d, 1H, J=5Hz) and 5.0 and 5.1 (s, each 1H). Compound XXV formed a monoacetate and could be oxidized to a ketone by sodium periodate. The ketone upon heating with aqueous sulfuric acid yielded formaldehyde. From these data the ester compound was assigned the structure XXV.

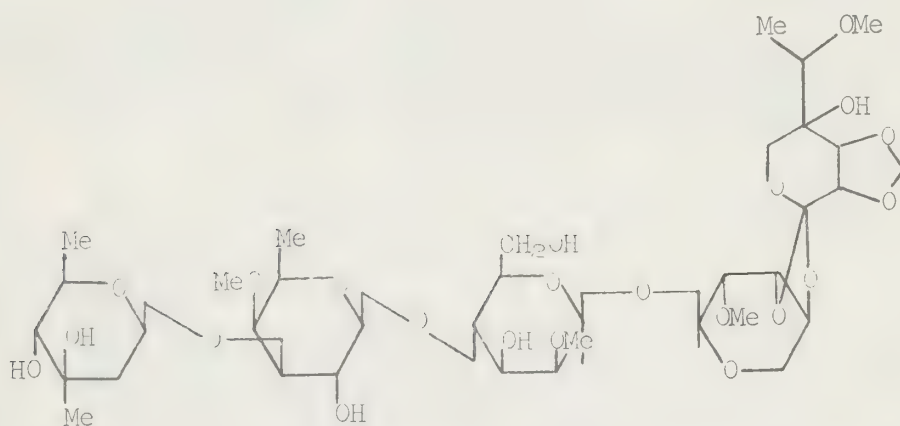
Permethylated oligose does not show the presence of any hydroxyl ester function in its ir spectrum. It yielded upon solvolysis compounds XVII and XXVI. The positions of the free hydroxyl groups in XVII were indicated by measuring the cd spectrum of the cuprammonium complex of XVII ([θ]₂₈₈ = -1250; suggesting K-chelate³⁰). The formation of a K-chelate is possible only if the hydroxyl groups of the 2-O-methyl lyxose moiety are free. Permethylated oligose on prolonged acidic hydrolysis yielded a mixture of products from which 2-O-methyl-L-lyxose (XI) was isolated confirming the above conclusion. These data indicate the formation of an ortho ester bond between evertetrose (XVI) and XXV to give the structure XXVII for oligose. The cmr spectrum of XXVII showed a signal at 119.8 ppm, thus confirming the presence of an ortho ester carbon in oligose.



XXV



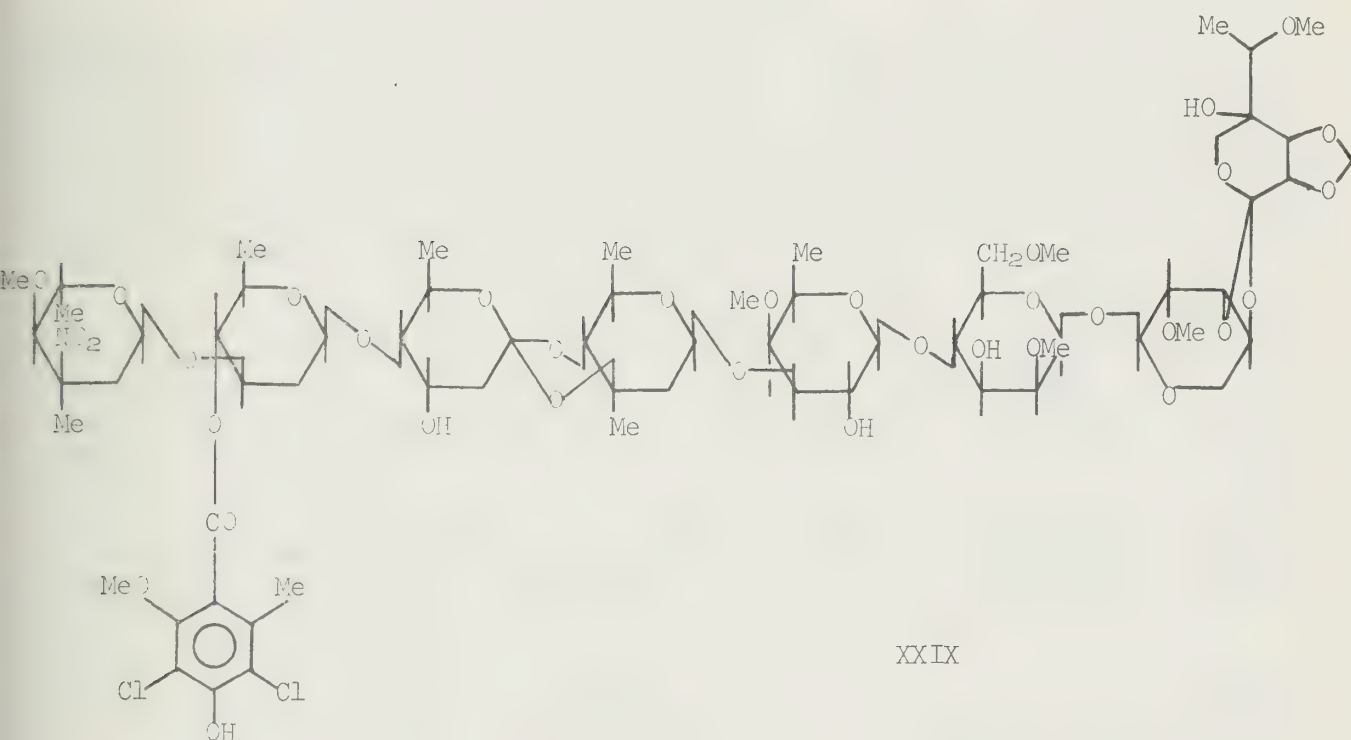
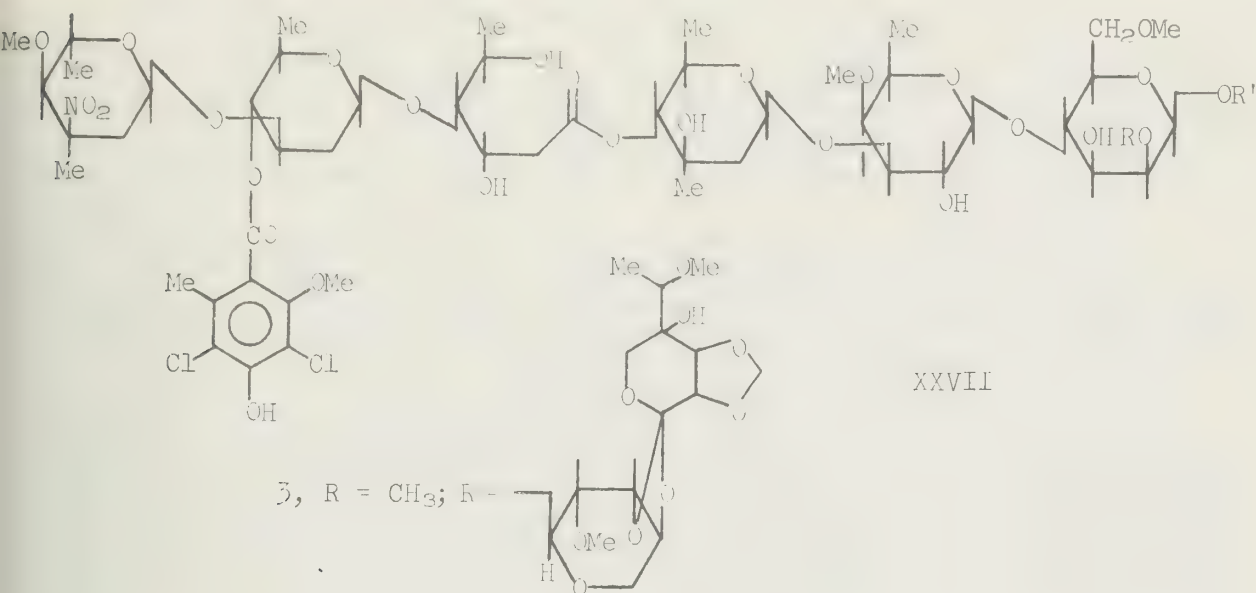
XXVI



XXVII

Everninomicin D₁ on hydrolysis yields everheptose (XXIV). As everninomicin D₁ and everheptose behave similarly in chemical reactions and particularly in their reaction with diazomethane, it follows that everninomicin D₁ must be represented by structure XXVIII. Permethylated everninomicin D on solvolysis yielded a mixture of products from which permethylated XIX and XVII' were isolated. The isolation of these two compounds indicates that the other two free hydroxyl groups in evermucose are involved in the linkage in the structure of everninomicin D. This is further confirmed by the isolation of V from the hydrolysis products of permethylated everninomicin D. Since everninomicin D on solvolysis did not yield any

products other than those recognized from the hydrolysis of everninomicin D₁, the conversion of everninomicin D to everninomicin D₁ involves the hydrolytic opening of an ortho ester linkage without loss of any component of the molecule. This latter ortho carbon atom was detected by cmr spectrum at 120.00 ppm. The final structure of everninomicin D was thus assigned by Ganguly and his coworkers as XXIX.



BIBLIOGRAPHY

1. H. Umezawa, K. Okawa, and M. Suzuki, *J. Antibiotics*, 8, 466 (1952).
2. O. L. Galmarini and V. Deulofeu, *Tetrahedron*, 15, 76 (1961).
3. R. Hütter, *Arch. Microbiol.*, 43, 23 (1962).
4. M. J. Weinstein, G. H. Wagman, I. M. Luedemann, and E. W. Oden, *Antimicrob. Agents Chemother.*, 24 (1964).
5. W. D. Ellis, C. Smith, and D. E. Wright, *Chem. Comm.*, 881 (1974).
6. A. K. Ganguly, O. Z. Sarre, D. Greeves, and J. Morton, *J. Am. Chem. Soc.*, 27, 1982 (1975).
7. G. H. Wagman, G. M. Luedemann, and M. J. Weinstein, *Antimicrob. Agents Chemother.*, 47 (1964).
8. G. M. Luedemann and B. Brodsky, *Antimicrob. Agents Chemother.*, 38 (1964).
9. J. Black, B. Calesnick, F. G. Faleo, and M. J. Weinstein, *Antimicrob. Agents Chemother.*, 38 (1964).
10. H. L. Herzog, E. Mesek, S. DeLorenzo, A. Murawski, W. Charney, and J. P. Rosselet, *Appl. Microbiol.*, 13, 515 (1965).
11. H. P. Faro and A. K. Ganguly, *Chem. Comm.*, 823 (1971).
12. H. Reimann, R. S. Jaret, and O. Z. Sarre, *J. Antibiotics*, 22, 131 (1968).
13. E. G. Gros, V. Deulofeu, O. L. Galmarini, and B. Frydmann, *Experientia*, 24, 323 (1968).
14. F. Buzzetti, F. Eisenberg, H. N. Grant, W. Keller-Schierlein, W. Voser, and H. Zähler, *Experientia*, 24, 320 (1968).
15. A. K. Ganguly, O. Z. Sarre, and H. Reimann, *J. Am. Chem. Soc.*, 90, 7129 (1968).
16. F. W. Lichtenthaler and P. Emig, *Tetrahedron Lett.*, 577 (1967).
17. D. M. Lemal, P. D. Pacht, and R. B. Woodward, *Tetrahedron*, 18, 1275 (1962).
18. A. K. Ganguly and O. Z. Sarre, *Chem. Comm.*, 1149 (1969).
19. W. Hofheinz, H. Grisebach, and H. Friebolin, *Tetrahedron*, 18, 1265 (1962).
20. A. K. Ganguly, O. Z. Sarre, and J. Morton, *Chem. Comm.*, 1488 (1969).
21. S. M. Partridge, *Nature*, 164, 443 (1949).
22. B. Helferich, L. Moog, and A. Junger, *Ber.*, 58, 872 (1925).
23. Prepared from D-lyxose; H. G. Walker, Jun. M. Gee, and R. M. McCready, *J. Org. Chem.*, 27, 2100 (1962).
24. W. Klyne, *Biochem. J.*, 47, XLI (1950).
25. A. K. Ganguly and O. Z. Sarre, *Chem. Comm.*, 911 (1970).
26. E. G. Gross, *Carbohydr. Res.*, 2, 56 (1966).
27. A. K. Ganguly, O. Z. Sarre, and S. Szmulewicz, *Chem. Comm.*, 746 (1971).
28. A. K. Ganguly, O. Z. Sarre, D. Greeves, and J. Morton, *J. Am. Chem. Soc.*, 95, 942 (1973).

CATION-ANION COMBINATION REACTIONS

Reported by Bruce D. Allison

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A complete understanding of acidity and basicity, the most fundamental of chemical properties, has eluded even the best chemists. Brønsted acid-base reactions, with their telltale protons, have yielded to a great deal of quantitative treatment. Although no one should be complacent about our knowledge of the proton and its doings, a far more complex problem is posed in the attempt to understand Lewis acid-base reactions quantitatively. Lewis bases and acids are labeled nucleophiles and electrophiles, respectively, and such will be the usage in this paper henceforth.

Several attempts to treat nucleophilic reactivities quantitatively have been made. The first, dealing primarily with S_N2 reactions of organic compounds, resulted in the Swain-Scott equation¹

$$\log k_x/k_{H_2O} = s n_x \quad (1)$$

where k_x is the second-order rate constant for reaction of the nucleophile (x) with electrophile; k_{H_2O} is the rate constant for reaction of water with the same electrophile; s is a parameter characteristic of the electrophile; and n_x is a parameter characteristic of the nucleophile. This equation was successful in correlating the reactions of nucleophiles with alkyl halides, but failed in more general applications.²

Edwards² has proposed a four parameter equation (eq 2) in an attempt to correlate the rates of nucleophilic substitution reactions with inorganic complexes, carbonyl compounds, and aromatic compounds, as well as S_N2 reactions.

$$\log k_x/k_{H_2O} = \alpha H + \beta E \quad (2)$$

Equation 2 relates the basicity, H , and the oxidation potential, E , of the nucleophile to its reactivity. The parameters α and β are measures of the sensitivity of the electrophile to these two properties of the nucleophile. A later modification³ of equation 2 substituted the polarizability of the nucleophile for the oxidation potential. Edwards' equation has had mixed success, one of the major disadvantages being, however, that E values are determinable for very few reagents.⁴

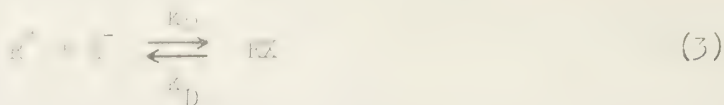
Pearson⁴ has proposed a more qualitative principle of "soft and hard acids and bases". Hard acids (R_3C^+ , H^+ , Li^+ , Na^+ , K^+ , Al^{3+}) prefer to react with hard bases (F^- , N^- , O^-) and soft acids (FeO , I_2 , Br_2) prefer to react with soft bases (S^- , Cl^- , Br^- , I^-). The polarizability of the species is taken as a criterion for its hardness or softness.

Selectivity-reactivity relationships have also been discussed.⁵⁻⁷ It has been maintained that as the reactivity of a reagent increases, its selectivity toward a series of reaction partners decreases. Unambiguous examples, however, have been difficult to find.^{8,9}

NUCLEOPHILIC REACTIVITIES TOWARD CATIONS

Significant advances in our understanding of nucleophilicity have been made through the study of the simple combination reactions of cations and anions to form covalent molecules.⁸ In an effort to investigate solvent and

structural effects on nucleophilic reactivities, Ritchie¹⁰⁻²² began a study of the rates of combination reactions between several stable organic cations and a variety of common nucleophiles (eq 3). His surprising observation was



that though the rates of reaction, k_2 , of various cations with a given nucleophile vary by a factor of 10^4 , and though the equilibrium constants for dissociation of the product, $K_D = k_D/k_2$, do not correlate, the selectivities of various cations toward a specific nucleophile were almost identical.¹⁴ A vast amount of data could be correlated by the use of a simple equation,¹⁸

$$\log k_N^R = \log k_{H_2O}^R + N_+ \quad (4)$$

where k_N^R is the rate constant for reaction of a particular cation with a given nucleophilic system (i.e. nucleophile and solvent), $k_{H_2O}^R$ is the pseudo-first-order rate constant for hydrolysis of the same cation in water, and N_+ is a parameter characteristic of the nucleophile and independent of the cation. Since k_N^R and $k_{H_2O}^R$ are easily found using conventional methods,¹⁰ N_+ values were defined in a given solvent by solving equation 4 using rate constants obtained from the reaction of p-nitro(Malachite Green) [bis(p-dimethylaminophenyl)-p-nitrophenylmethyl] cation with the appropriate nucleophile. Table 1⁸ lists N_+ values for several common nucleophiles. Figure 1⁸

Table 1. N_+ Values for Nucleophilic Systems at 23°.

Nucleophile (solvent)	N_+	Nucleophile (solvent)	N_+	Nucleophile (solvent)	N_+
H ₂ O (H ₂ O)	0.0	N ₃ ⁻ (H ₂ O)	5.4	CN ⁻ (DMF)	9.4
MeOH (MeOH)	0.5	CN ⁻ (MeOH)	5.9	N ₃ ⁻ (Me ₂ SO)	10.7
CN ⁻ (H ₂ O)	3.8	CH ₃ O ⁻ (MeOH)	7.5	C ₆ H ₅ S ⁻ (MeOH)	10.7
C ₆ H ₅ SO ₂ ⁻ (MeOH)	3.8	N ₃ ⁻ (MeOH)	6.5	C ₆ H ₅ S ⁻ (Me ₂ SO)	13.1
OH ⁻ (H ₂ O)	4.5	CN ⁻ (Me ₂ SO)	8.6		

illustrates the quality of some of the correlations. p-DAMPhTr⁺ is p-dimethylaminophenyltropylium ion. The solid lines shown in Figure 1 have unit slope as required by equation 4 up to k_N^R values of $10^{10} \text{ M}^{-1} \text{ sec}^{-1}$, and then have zero slope since the rates are diffusion controlled.¹⁸

SUCCESSSES

Triarylmethyl cations. Malachite Green [4,4'-bis(dimethylamino)-triphenylmethyl tetrafluoroborate], Crystal Violet [4,4',4''-tris(dimethylamino)-triphenylmethyl tetrafluoroborate] and p-Nitromalachite Green [4,4'-bis(dimethylamino)-4''-nitrotriphenylmethyl tetrafluoroborate] were found to react with cyanide, azide, hydroxide, deuterioxide, and methoxide ions at the methyl carbon in water, methanol, DMSO, DMF, and D₂O to give covalently bonded products.¹⁰ In each case, equation 4 correlated the second-order rate constants obtained (Figure 1). Equilibrium constants for the dissociation

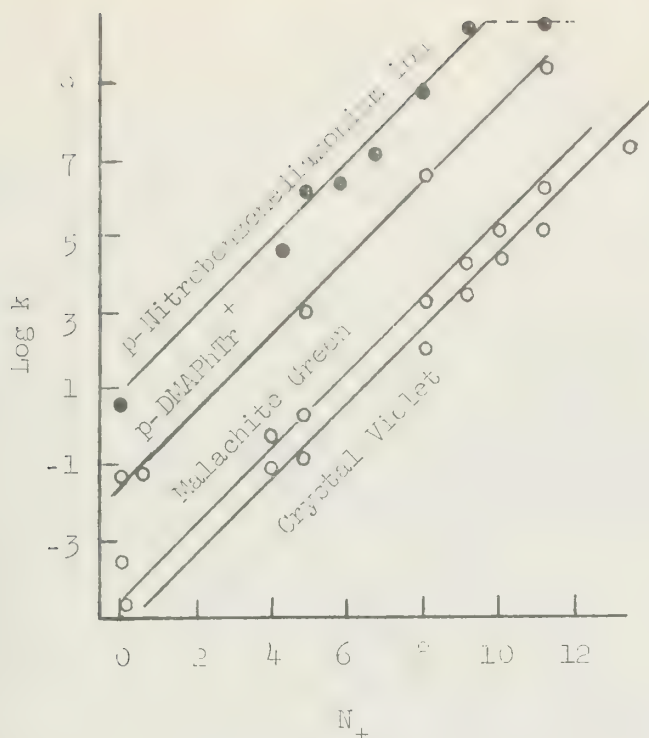
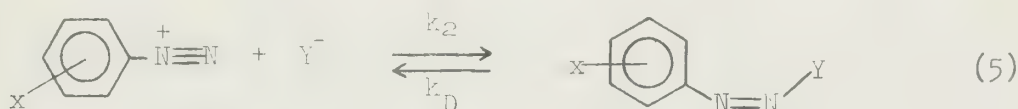


Figure 1. The correlation of rates of cation-nucleophile reactions by eq 4.

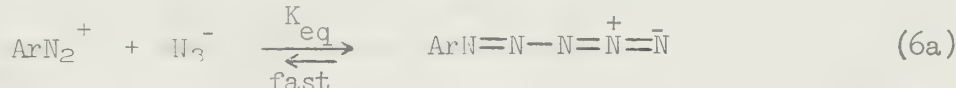
of products did not correlate with each other, or with second-order rate constants. The unique nucleophilic reactivity sequence $\text{N}_3^- > \text{CH}_3\text{O}^- > \text{CN}^-$ was observed. Since cyanide is both more basic and more polarizable than azide ion, Edwards' equation failed to predict the observed sequence.

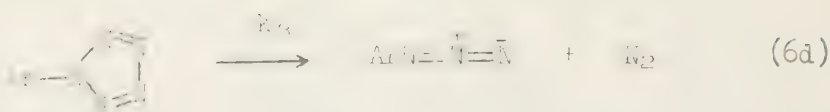
Diazonium ions. The rates of disappearance of some substituted diazonium ions (eq 5) upon reaction with water and hydroxide, cyanide, methoxide, azide, cyanide, and thiophenoxide ions were measured in aqueous solution,¹¹⁻¹³ in methanol,¹⁴ and in DMSO.¹⁸



$\text{X} = \text{p-NO}_2, \text{p-CN}, \text{m-CF}_3, \text{m-Cl}, \text{p-Br}, \text{p-Cl}, \text{p-CO}_2^-, \text{H}, \text{p-CH}_3$

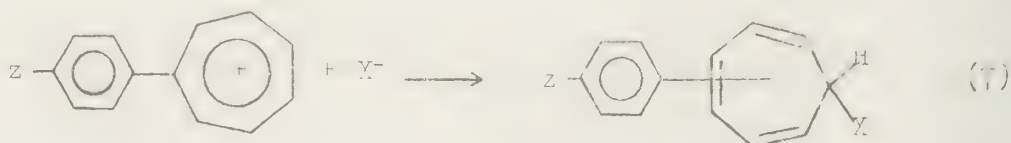
Nucleophilic reactivities in such reactions were also found to be correlated well by equation 4,¹⁸ with the exception of azide ion in aqueous solution. Hammett plots for the formation of syn-diazohydroxides and syn-diazocyanides give ρ values of ca. 2.4, however, while ρ values for the reaction of azides with aryl diazonium ions are ca. 3.2.¹³ Comparison with the ρ value of 3.53 for the equilibrium formation of syn-diazocyanides led to the conclusion that azide reactions involve a rapid preequilibrium formation of the diazoazide, followed by rate-determining decomposition to arylazide and pentazole¹² (eq 6).





Thus, equation 4 could not be applied to the reaction of azide ion with aryldiazonium ions in aqueous solution.

Tropylium ions. Nucleophiles react with tropylium ions as shown, where four isomeric products are possible (eq. 5). Reactions of water and hydroxide in water,¹⁶ and methanol, methoxide, azide, and thiophenoxide in methanol¹⁷ with these cations also obeyed equation 4.



z = p-(CH₃)₂N, p-CH₃O, H, p-Cl

Reactions of amines with cations. Ritchie²⁰ has extended the use of equation 4 from correlations of the nucleophilicities of primarily mononegative anions to the reactivities of amines with the previously studied cations. The rates of reactions of a wide variety of amines (Figure 2) with Malachite Green, p-Nitromalachite Green, p-dimethylaminophenyltropylium ion, and tropylium ion were found to be nicely correlated by equation 4 (Figure 2). New N_+ values for amines were calculated using equation 8,

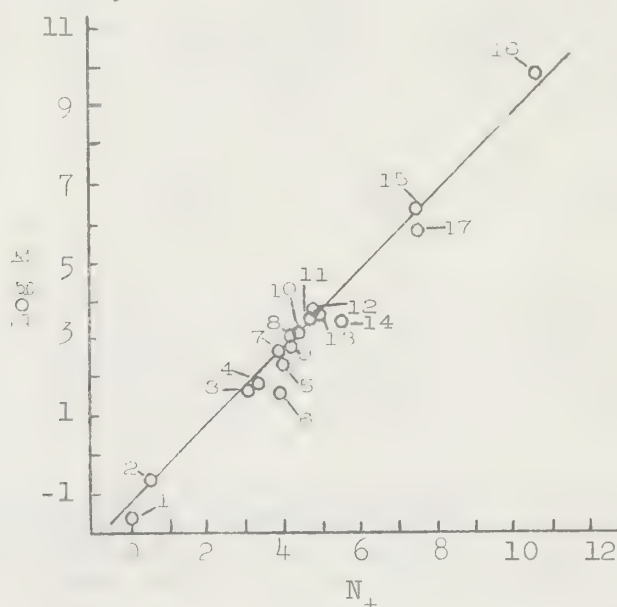
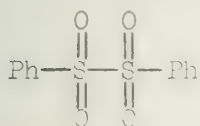


Figure 2. Rates of reactions of p-dimethylaminophenyltropylium ion plotted according to eq 4. The points are identified as follows: (1) H₂O; (2) CH₃OH; (3) 2,2,2-trifluoroethylamine; (4) semicarbazide; (5) 2-ammonioethylamine; (6) methoxylamine; (7) glycine ethyl ester; (8) glycylglycine; (9) phenylhydrazine; (10) hydroxide ion; (11) ethylamine; (12) glycine; (13) ethylenediamine; (14) hydrazine; (15) methoxide ion (in methanol solution); (16) thiophenoxide ion (in methanol solution); (17) sulfite ion.

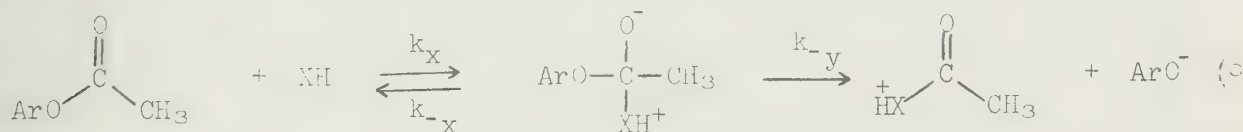
$$\log k_{\text{MG}} = -4.00 + N_+ \quad (8)$$

where k_{MG} is the rate constant for the reaction of Malachite Green with the nucleophile, and -4.00 is the log of the rate constant for reaction of Malachite Green with water. Reactions of aryl diazonium ions with amines failed to give kinetics that were first order in amine, and were abandoned due to the small probability of obtaining the desired rate constants for the simple combination step.²⁰

Esters. Jencks^{23,25} has accumulated an extensive body of kinetic data for the reactions of nucleophiles with acetate esters. The application of equation 4 to these reactions^{20,22} gave reasonable correlations for 1-acetoxy-4-methoxypyridinium perchlorate (AMPP) and for 2,4-dinitrophenylacetate (DNPA), but failed to correlate reactions of p-nitrophenyl acetate (PNPA) and phenyl acetate (PA) with nucleophiles. Kice²⁶ has observed that reactions of nucleophiles with phenyl- α -disulfone (PDS) 1 correlate well with reactions of the same nucleophiles with AMPP and hence must obey equation 4.



1
Reactions of aryl acetates with nucleophiles, however, have been postulated to proceed by a simple two-step mechanism uncomplicated by proton transfer from the intermediate^{24,25,27} (eq 9). In the two-step mechanism shown, equation 4 should apply only if attack of the nucleophile is rate determining.²³



Application of the Bodenstein approximation to this reaction scheme gives

$$k_{\text{obsd}} = k_x / [1 + k_{-x}/k_{-y}] \quad (10)$$

for the observed second-order rate constant of the reaction. If k_x , the rate constant for the combination step, is correlated by equation 4, substitution of equation 4 into equation 10 should give an equation that correlates the second-order rate constants with N_+ values (eq 11).

$$\log k_{\text{obsd}} = \log k_o + N_+ - \log [1 + k_{-x}/k_{-y}] \quad (11)$$

Evaluation of the quantity k_{-x}/k_{-y} , then, is necessary. This was done by utilizing data fitting procedures. The evaluation of k_{-x} and k_{-y} was restricted by requiring the relative value of k_{-x} to be independent of the identity of the ester.

New N_+ values were evaluated by iterative averaging of the N_+ and $\log k_o$ parameters from plots for the previously examined reactions according to equation 4. The $\log k_o$ value for Malachite Green was arbitrarily set equal to -4.13 to preserve the approximate magnitudes of the previously reported numbers. Estimates of $\log k_o$ and $\log k_{-x}$ for several reactions allowed calculation of $\log k_{-y}$. An iterative procedure involving incrementing $\log k_{-x}$ values and minimizing the sum of the squares of the deviations from

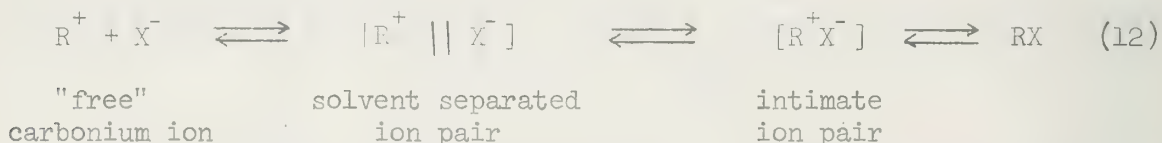
equation 11, calculation of new k_o values using new k_{-x} and k_{-y} values, followed by further iteration, gave k_o , k_{-x} , and k_{-y} values. A complete table of N_+ values and $\log k_{-x}$ values for nucleophiles, and k_o and k_{-y} values for electrophiles thus obtained is included in reference 22.

Correlations found according to equation 11 were excellent. Of 382 rate constants examined, only 24 were found to deviate by more than 1 log unit, and another 23 deviated by 0.5 to 1.0 log unit. The high quality of the correlations was taken to provide strong support for the assumed mechanism.²¹ It has been argued that the leaving group ability of an aryl oxide should depend on the driving force exerted by a lone pair of electrons on another group in the tetrahedral intermediate.²⁸ Since a single scale of $\log k_{-x}$ terms was employed in Ritchie's study, such an argument is suspect.

According to the present analysis,²² the attack of the nucleophile on the ester is rate determining for those cases where $\log k_{-y}$ is greater than $\log k_{-x}$, and the breakdown of the tetrahedral intermediate is rate determining in those cases where $\log k_{-x}$ is greater than $\log k_{-y}$.

GENERAL IMPLICATIONS

As mentioned before, there has been no evidence for a correlation between rate and equilibrium constants for the nucleophile-electrophile reactions.⁸ Also, equilibrium constants for a series of nucleophiles reacting with one electrophile vs. those for another electrophile are not related. These observations led to the speculation that steric and specific bonding effects present in the products are not present at the transition state, and thus nucleophile and electrophile are separated by large distances at the transition state. In terms of Winstein's mechanism²⁹ for the S_N1 solvolysis reaction (eq 12), the transition state for the rate determining step lies between the intimate and solvent separated ion pairs.



This speculation has been contradicted by the observation of large Brønsted slopes (β values of ca. 0.5) for the reactions of amine nucleophiles with cations²² (plots of N_+ for the amines vs. pK_a of the amine conjugate acids have large slopes, β). β is taken to indicate the degree of resemblance of the transition state to the product, or the degree of bond formation in the transition state.³⁰

Ritchie⁸ has also observed that the relative rates of reaction of cations are independent of solvent, while equilibrium constants are not. These data led to the postulate that the solvent shell of the cation at the transition state is nearly the same as that of the reactant cation, and that the interactions between electrophile and nucleophile at the transition state are long-range coulombic attractions. However, anionic, cationic (DABCOH⁺), and neutral nucleophiles reacting with both neutral and cationic electrophiles, show the same orders of reactivity,²² making such an argument improbable.

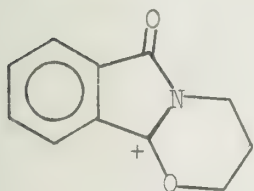
The observation that the relative reactivities of nucleophiles are solvent dependent along with the aforementioned postulates concerning the transition state, led to the conclusion that N_+ values were an inherent property of the nucleophile, and represented the desolvation energies of the nucleophiles. The Brønsted slopes for the amine reactions,²² and the fact that amines are relatively unreactive compared to other nucleophiles of similar basicity, have also rendered this conclusion suspect.

At present Ritchie has offered no rationale for his empirical observations. Significant work remains to be done in describing the fundamental factors responsible for such a seemingly general and simple correlation.

PROBLEMS

General base catalysis. N_+ values were originally calculated using the reactions of cations with water as the standard reaction¹⁸ (eq 4). Since that time it has been shown by a number of workers^{19,21,31-33} that the reactions of water with stable cations are anomalous. Even though water does not obey the N_+ correlations,²¹ since the N_+ scale is a relative scale of reactivities, the correlations are still valid.

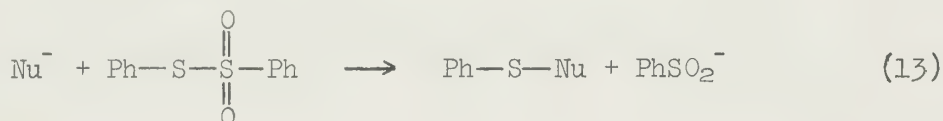
Ritchie^{19,21} has shown that the reactions of triarylmethyl cations with water exhibit general base catalysis with DABCO (diazabicyclo-[2.2.2]-octane) and triethyl amine. A Brønsted coefficient of ca. 0.5 is found for such base catalysis. Wyatt³¹ has demonstrated that the reaction of tri-*p*-anisylmethyl cation with water is catalyzed by DABCO, triethylamine, and trimethylamine. Solvolyses of benzhydryl derivatives in aqueous organic solvents also appear to exhibit general base catalysis.³³ Jencks³² has reported that the reactions of *N*,*O*-trimethylenephthalimidium cations 2 with water in aqueous media exhibit general base catalysis by DABCO, while reactions with amines do not. The ratio k_{H_2O}/k_{DABCO} was found to be 0.13 M.



2

Ritchie²¹ has found that the ratio k_{OH^-}/k_{H_2O} for reaction of hydroxide with a series of triarylmethyl cations in water varied widely, and that hydroxide appeared to obey the N_+ correlations. The ratio k_{H_2O}/k_{DABCO} , however, was nearly constant [0.12 for Crystal Violet, 0.082 for Malachite Green, 0.12 for *p*-methyl-*p*'-dimethylaminotriphenylmethyl cation, and 0.06 for *p*-trifluoromethyl(Malachite Green)], agreed with Jencks' value for 2, and indicated that the uncatalyzed water reaction is similar to the general base catalyzed reaction. Least squares fits of $\log k_2$ vs. $1/T$ gave large negative entropies of activation (ΔS^\ddagger) for the reactions of Malachite Green and Crystal Violet with cyanide and hydroxide. This was taken to imply that the solvent must be more ordered at the transition state than at either reactant or product.²¹

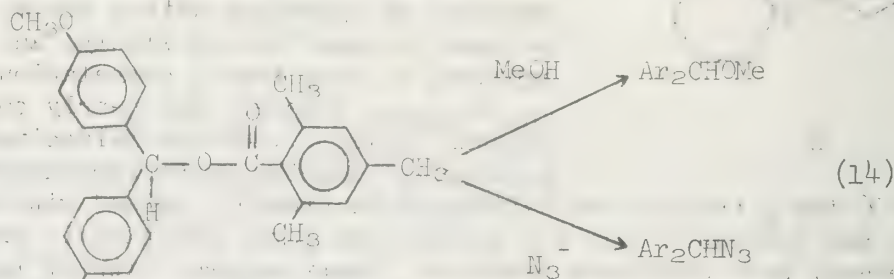
Reactions of phenylbenzenethiosulfonate with nucleophiles. Kice³⁴ has studied the reactions of phenylbenzenethiosulfonate with a variety of amines and anionic nucleophiles (eq 13).



He has found that nitrogen-based nucleophiles correlate well with Ritchie's N_T values; anionic nucleophiles Me^- , CN^- , $\text{C}_6\text{H}_5\text{CH}_2\text{O}^-$, HO^- , and $\text{CH}_3\text{CONHO}^-$ are scattered but not seriously; and CN^- and $n\text{-BuS}^-$ deviate seriously (ca. 15 units), in contrast to reactions with the phenyl- α -disulfone 1.²⁶ Two possible explanations are offered. First, Kice suggests that for center where solvent solvation of the nucleophile does not determine nucleophilic reactivity, eq. 4 will fall. Second, he suggests that the reaction of phenylbenzenethiosulfonate with nucleophiles may differ mechanistically from the reaction of phenyl- α -disulfone with nucleophiles. For the former, the rate determining step may be formation of the nucleophile-S bond, synchronously with cleavage of the S-S bond, or even rate determining cleavage of the S-S bond, while for the former, the rate determining step always involves formation of the Nu-SO₂ bond.

Stability-reactivity relationships. Chemists have long intuitively believed that highly reactive substances should be indiscriminate in their choice of reactants.⁹ The widely accepted Hammond postulate⁵ is a formal statement of this assumption. Sneath⁶ and Schleyer,²⁰ in particular, have attempted to quantify such behavior for carbonium ion reactions with nucleophiles. Ritchie's observations run counter to these postulates.

The validity of stability-reactivity relationships has been questioned by Kemp⁸ for fractional increases in reactivity of a species within a given rate range. Several workers have invoked ion pairing effects to explain observed differences in selectivity.^{10,30} Ritchie,¹⁵ for example, has concluded that trapping studies in the case of competitive attack on *p*-toluenedimethoxybenzhydrylacetate by azide and methanol in methanol (eq. 14) indicate that two intermediates, the ion pair and the carbonium ion, are being trapped. He suggests that the ion pair is less selective than the carbonium ion, and that many of the selectivity-reactivity relationships observed for $\text{S}_{\text{N}}1$ solvolyses are really variations in the proportion of product arising from free ions and ion pairs from various reactants. The question of stability-reactivity relationships is far from resolved, however, and warrants further investigation.



BIBLIOGRAPHY

1. C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).
2. J. D. Edwards, *ibid.*, **76**, 1549 (1954); **78**, 1819 (1956).
3. J. D. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).
4. R. G. Pearson, H. Sobel, and J. Songstad, *ibid.*, **90**, 319 (1968).
5. G. S. Hammond, *ibid.*, **77**, 334 (1955).
6. R. A. Sneath, J. V. Carter, and P. S. Kay, *ibid.*, **88**, 2594 (1966).
7. J. M. Harris, D. C. Clark, A. Becker, and J. F. Fagan, *ibid.*, **96**, 4478, 4484 (1974).

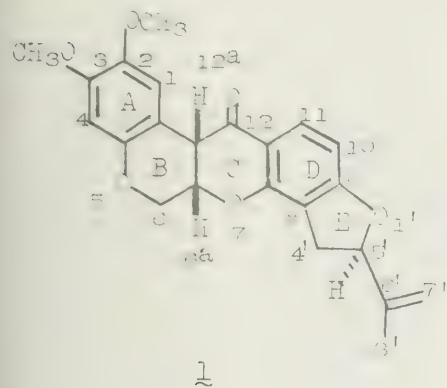
8. C. D. Ritchie, *Accts. Chem. Res.*, 2, 514 (1969).
9. D. S. Kemp and M. L. Casey, *J. Am. Chem. Soc.*, 95, 6670 (1973).
10. C. D. Ritchie, G. A. Skinner, V. G. Badding, *ibid.*, 89, 2063 (1967).
11. C. D. Ritchie and D. J. Wright, *ibid.*, 93, 2425 (1971).
12. C. D. Ritchie and D. J. Wright, *ibid.*, 93, 2429 (1971).
13. C. D. Ritchie and D. J. Wright, *ibid.*, 93, 6574 (1971).
14. C. D. Ritchie and P. O. I. Virtanen, *ibid.*, 94, 1589 (1972).
15. C. D. Ritchie, *ibid.*, 93, 7324 (1971).
16. C. D. Ritchie and H. Fleischhauer, *ibid.*, 94, 3481 (1972).
17. C. D. Ritchie and P. O. I. Virtanen, *ibid.*, 94, 4963 (1972).
18. C. D. Ritchie and P. O. I. Virtanen, *ibid.*, 94, 4966 (1972).
19. C. D. Ritchie, *ibid.*, 94, 3275 (1972).
20. C. D. Ritchie and P. O. I. Virtanen, *ibid.*, 95, 1882 (1973).
21. C. D. Ritchie, D. J. Wright, Der-shing Huang, and A. A. Kamege, *ibid.*, 97, 1163 (1975).
22. C. D. Ritchie, *ibid.*, 97, 1170 (1975).
23. W. P. Jencks and M. Gilchrist, *ibid.*, 90, 2622 (1968).
24. A. R. Fersht and W. P. Jencks, *ibid.*, 92, 5442 (1970).
25. D. G. Oakenfull and W. P. Jencks, *ibid.*, 93, 178, 188 (1971).
26. J. L. Kice and E. Legan, *ibid.*, 95, 3912 (1973).
27. W. P. Jencks and K. Salvesen, *ibid.*, 93, 1419 (1971); J. P. Fox, M. I. Page, A. Satterthwaite, and W. P. Jencks, *ibid.*, 94, 4729 (1972); 96, 7018, 7031 (1974).
28. N. Gravetz and W. P. Jencks, *ibid.*, 96, 489, 499, 507 (1974).
29. S. Winstein, P. E. Klinedinst Jr., and G. C. Robinson, *ibid.*, 83, 885 (1961).
30. J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 241.
31. J. H. Ride, P. A. Wyatt, and Z. M. Zochowski, *J. Chem. Soc., Perkin Trans.*, 2, 1188 (1974).
32. W. P. Jencks and N. Gravitz, *J. Am. Chem. Soc.*, 96, 489, 499 (1974).
33. H. L. Goering, R. G. Briody, and J. F. Levy, *ibid.*, 85, 3059 (1963); H. L. Goering and H. Hopf, *ibid.*, 93, 1224 (1974).
34. J. L. Kice, T. E. Rogers, and A. C. Warheit, *ibid.*, 96, 8020 (1974).
35. D. J. Raber, S. M. Harris, R. E. Hall, and P. v. R. Schleyer, *ibid.*, 93, 4821 (1971).
36. C. J. Collins and B. J. Benjamin, *J. Org. Chem.*, 37, 4358 (1972); C. J. Collins, *Accts. Chem. Res.*, 4, 315 (1970).

CHEMISTRY OF THE ROTENOIDS

Reported by Robert J. McGorrin

November 17, 1977

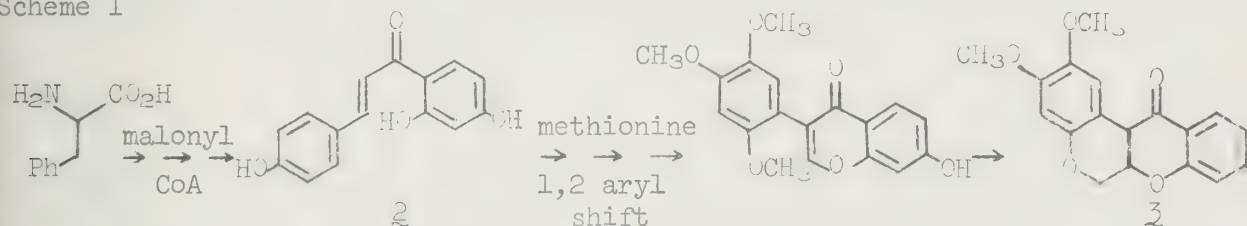
The rotenoids¹ are a class of fish poisons and insecticidal constituents isolated from the roots and seeds of various leguminous plants including the genera *Derris*, *Lonchocarpus*, *Milletia*, and *Tephrosia*, of which rotenone (**1**) is the most abundant and effective toxic principle. Rotenone preparations exhibit low mammalian oral toxicity.^{2,3} Enzyme studies with NADH-linked substrate demonstrated that rotenone inhibits electron transport by blocking oxygen utilization at the cytochrome *b* stage.² Structure-activity relationships have been considered.^{2c,3}



Rotenone was first isolated as a white crystalline substance from *L. (Robinia) nicou* by Geoff in 1895. The basic molecular structure was determined in 1932, and in 1961 the absolute stereochemistry was assigned. All naturally occurring rotenoids possess the basic chromanochromanone skeleton; variations in structure include 5- and 6-membered ring E modified compounds,⁴ and combinations of hydroxylation and oxygenation at the 6, 8', 11, and 12 positions.⁵ As evidenced by a similar positive Cotton effect or their ORD curves, all rotenoids possess a $\alpha\beta$, $12\alpha\beta$ configuration.^{5a,6} The preferred molecular conformation was established by proton and C-13 NMR studies.⁷

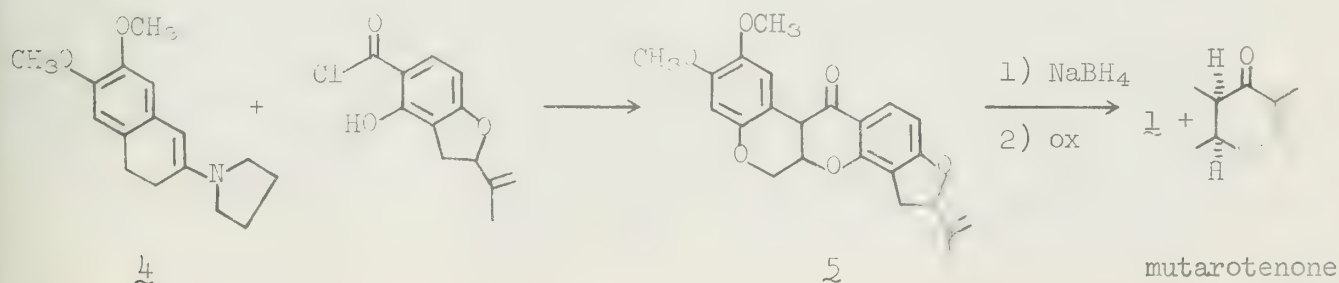
Studies on the biosynthesis of rotenoids have been shown to parallel that of isoflavones.⁸ Rotenone biogenesis is proposed to occur by condensation of a phenylalanine-derived precursor with malonyl-CoA to produce the chalcone **2**, followed by an aryl migration via a postulated spirodienone intermediate.^{9a} (Scheme I) In nature there is evidence that the conversion of isoflavones into rotenoids employs S-adenosylmethionine to effect methylene insertion in the completion of ring B.^{9b} 9-Demethylmunduserone (**3**) is implicated as a key biosynthetic rotenone precursor,^{9c} with ring E formation occurring in post-rotenoid stages by isoprenylation, cyclization, and dehydration.

Scheme I



The first formal synthesis of rotenone was reported by Miyano and Matsui¹⁰ which produced the immediate precursor of rotenone, *dl*-derrisic acid, in low yield. A successful total synthesis of rotenone employed condensation of the pyrrolidine enamine^{11a} **4** with tubaic acid chloride to afford dehydrorotenone (**5**) (Scheme II), which can undergo successive reduction and Oppenauer oxidation¹² to give a mixture of stereoisomers. The dehydrorotenone skeleton can be constructed by a similar

Scheme II



method utilizing Hoesch condensations between the appropriate nitriles and resorcinol derivatives,¹³ thermal condensations of β -keto esters with phenols,¹⁴ polyphosphoric acid acylations of phenols with isoflavone derivatives,¹⁵ and by hydrolysis of phenoxyacetic acid isoflavone derivatives.¹⁶ A novel synthesis of rotenoid which does not require reduction of the rotenone intermediate proceeds via acetylenic intermediates.¹⁷ Crombie¹⁸ developed a new method paralleling biogenesis which employs a trimethylsilyl diazomethane to effect a one carbon insertion in isoflavone intermediates.

BIBLIOGRAPHY

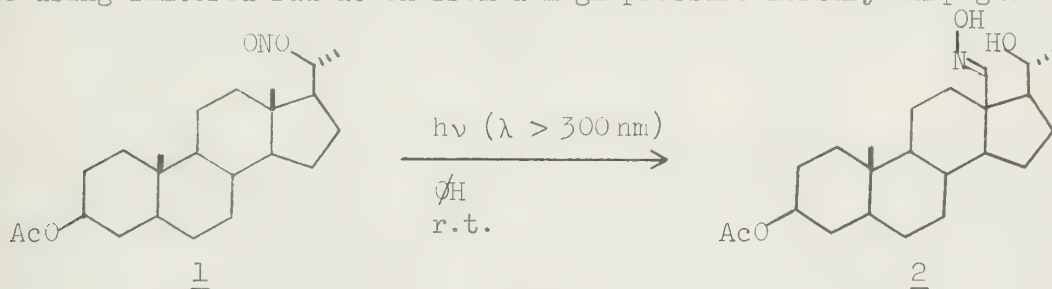
1. Reviews: (a) L. Crombie, *Fortschr. Chem. Org. Naturstoffe*, 21, 275 (1963); (b) A. Mustafa, Ed., "The Chemistry of Heterocyclic Compounds," Vol. 23, Interscience Pub., New York, 1967, pp 272-327; (c) F. M. Dean in "The Total Synthesis of Natural Products," Vol. I, J. ApSimon, Ed., John Wiley & Sons, New York, 1973, pp 498-513.
2. (a) J. Fukami, I. Yakamoto, and J. E. Casida, *Science*, 155, 713 (1967); (b) D. J. Horgan, T. P. Singer, and J. E. Casida, *J. Biol. Chem.*, 243, 834 (1968); (c) I. Yamamoto in "Annual Review of Entomology," R. F. Smith, Ed., Vol. 15, Annual Reviews, Inc., Palo Alto, Ca., 1970, pp 257-272.
3. (a) T. Unai, H. Cheng, I. Yamamoto, and J. E. Casida, *Agr. Biol. Chem.*, 37, 1937 (1973); (b) J. Sarma, G. Srimannarayana and N. Subba Rao, *Indian J. Chem.*, 13, 228 (1975).
4. M. Krishnamurthi, Y. R. Sambhy, and T. R. Seshadri, *Tetrahedron*, 26, 3023 (1970).
5. (a) T. Unai, I. Yamamoto, H. Cheng, and J. Casida, *Agr. Biol. Chem.*, 37, 387 (1973); (b) D. Shienghong, T. Donovanik, V. Uaprasert, and S. Roengsumran, *Tetrahedron Lett.*, 2015 (1974); (c) M. E. Oberholzer, C. J. H. Rall, and D. G. Roux, *ibid.*, 2211 (1974).
6. C. Djerassi, W. D. Ollis, R. C. Russell, *J. Chem. Soc.*, 1448 (1961).
7. (a) D. G. Carlson, D. Weisleder, and W. H. Tallent, *Tetrahedron*, 29, 2731 (1973); (b) L. Crombie, G. Kilbee, and D. A. Whiting, *J. Chem. Soc. Perkin I*, 1497 (1975).
8. W. D. Ollis in "Symposium on Phytochemistry," H. R. Arthur, Ed., Hong Kong University Press, 1964, pp 128-138.
9. (a) P. M. Dewick, *Zeitschrift fur Physiol. Chemie*, 353, 132 (1972); (b) L. Crombie, P. M. Dewick, and D. A. Whiting, *Chem. Comm.*, 1469 (1970); (c) L. Crombie, P. M. Dewick, and D. A. Whiting, *J. Chem. Soc., Perkin I*, 1285 (1973).
10. (a) M. Miyano, A. Kobayashi, and M. Matsui, *Agr. Biol. Chem.*, 24, 540 (1960); (b) *ibid.*, 25, 673 (1961).
11. (a) M. Miyano, *J. Amer. Chem. Soc.*, 87, 3958, 3962 (1965); (b) M. Miyano, *J. Org. Chem.*, 35, 246 (1970); (c) M. Uchiyama, M. Ohhashi, and M. Matsui, *Agr. Biol. Chem.*, 30, 1145 (1966); (d) N. Nakatani and M. Matsui, *ibid.*, 39, 529 (1975).
12. M. Miyano and M. Matsui, *Bull. Agr. Chem. Soc. Japan*, 22, 128 (1958).
13. (a) D. J. Ringshaw and H. J. Smith, *J. Chem. Soc. (C)*, 102 (1968); (b) F. Fujita, N. Nakatani, and M. Matsui, *Agr. Biol. Chem.*, 37, 1737 (1973).
14. (a) M. Baran-Marsak, J. Massicot, and D. Molko, *Bull. Soc. Chim. France*, 191 (1971); (b) R. Verhé and N. Schamp, *Bull. Soc. Chim. Belg.*, 82, 283 (1973).
15. (a) N. Nakatani and M. Matsui, *Agr. Biol. Chem.*, 32, 769 (1968); (b) R. Verhé, N. Schamp, and M. Sadones, *Experientia*, 31, 266 (1975).
16. (a) K. Fukui, M. Nakayama, and T. Harano, *ibid.*, 23, 613 (1967); (b) V. Chandrashekar, M. Krishnamurthi, and T. R. Seshadri, *Tetrahedron*, 23, 2505 (1967).
17. (a) H. Omokawa and K. Yamashita, *Agr. Biol. Chem.*, 37, 195 (1973); (b) *ibid.*, 37, 1717 (1973); (c) *ibid.*, 38, 1731 (1974); (d) H. Omokawa, S. Kouya, and K. Yamashita, *ibid.*, 39, 393 (1975).
18. (a) L. Crombie, P. W. Freeman, and D. A. Whiting, *Chem. Comm.*, 563 (1970); (b) *ibid.*, *J. Chem. Soc. Perkin I*, 1277 (1973).

THE BARTON REACTION - SITE SPECIFIC FUNCTIONALIZATION OF UNACTIVATED CENTERS

Reported by John Zeigler

November 20, 1975

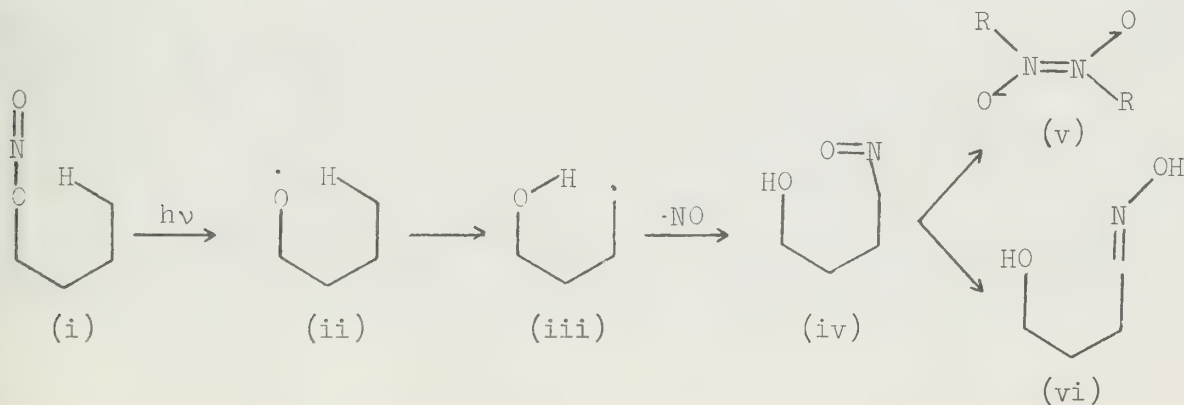
The functionalization of specific unactivated carbon atoms has long been a central problem in synthesis. Reagents powerful enough to introduce functions at unactivated carbons have typically exercised such low selectivity that such routes are not generally useful in synthesis, although some special cases where steric factors could be employed to direct their action are known. In the last fifteen years, however, progress in this area has come through the discovery and use of a number of new reactions, mainly photochemical in nature, which have in common the ability to functionalize unactivated centers via intramolecular attack of a heteroatom radical on a nearby C-H bond. The most well-known and probably the most useful of these reactions is the Barton reaction. In 1960, Barton and coworkers found^{1a,b} that photolysis of the nitrite 1 in dry benzene using filtered radiation from a high-pressure mercury lamp gave the



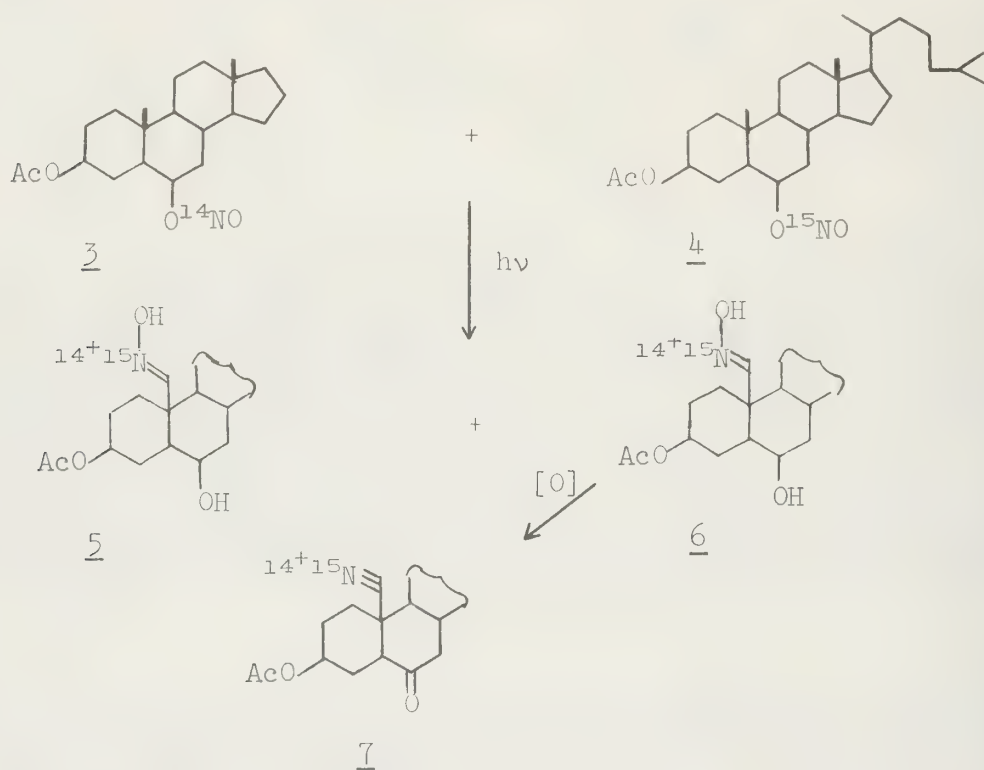
γ -oximino derivative 2. In the period since its discovery, the Barton reaction has become a much-studied and very useful method for the chemist. Its success has inspired the development of several alternative methods which are mechanistically similar. Intramolecular functionalization reactions have been observed for hypohalites,² N-halo³ and N-nitroso amides,⁴ and nitrates⁵ on photolysis and on treatment of alcohols with lead tetraacetate.² Although a variety of photolabile groups are available for intramolecular functionalizations, the most well-explored, readily available, and widely-used is the nitrite function. The Barton reaction of organic nitrites will be the topic of this seminar. Information on the analogous reactions of other groups may be found in one of the excellent reviews^{2,6,14} in the area.

Mechanism

In their original article,^{1b} Barton and coworkers proposed that, upon irradiation, homolysis of the O-N bond in the nitrite(i) occurs to give nitric oxide and an alkoxy radical(ii) which then abstracts a hydrogen atom from the γ -carbon via a six-membered transition state. Reaction of the resulting carbon radical(iii) with NO gives the γ -nitrosoalcohol(iv) which may either dimerize if sterically unhindered(v) or undergo tautomerization to the γ -oximino alcohol(vi).

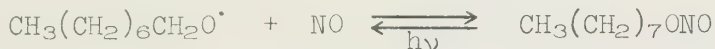


Barton found that a change of solvent to toluene, a more efficient radical trap, affected the yield very little, indicating that trapping of the alkoxyl or carbon radical by NO was very rapid. This was originally interpreted by Barton as evidence for solvent cage formation and trapping of NO; however, it was found that addition of two equivalents of NO to the photolysis mixture greatly suppressed product formation, apparently due to rapid reversal of the initial homolysis. The final proof of a non-cage mechanism was supplied by Akhtar and Pechet.^{1,2} Partial photolysis in toluene of a mixture of 3 β -acetoxy-androstan-6 β -yl nitrite (3) and 3 β -acetoxy-cholestan-6 β -yl nitrite (4) labeled with 98.3% ¹⁵N gave the oximes 5 and 6. Mass spectral analysis of the ketonitrile 7 formed by oxidation of 6 gave a ¹⁵N:¹⁴N ratio of 1.15:1.00. Isolation and mass spectral analysis of unreacted 4 showed no loss of label. Since the initial formation of the alkoxyl is known to be reversible from quantum yield studies, randomization of the label must have occurred after hydrogen transfer in a non-cage process. As we shall see later, this result has been put to use in improving the synthetic flexibility of the Barton reaction.



In a series of excellent papers, Kabasakalian, Townley, and Yudis reported the results of a systematic study of the photolysis reactions of a series of alkyl, alkyl aromatic, and alicyclic nitrites. They found⁷ that photolysis of 1-octyl nitrite in heptane gave a 30% yield of 4-nitroso-1-octanol dimer, 2% yield of a mixture of isomeric nitrosoheptane dimers, and a 13% yield of mixed nitrosoheptane-4-nitroso-1-octanol dimer. No other isomeric nitrosooctanols were found. The 4-nitroso-1-octanol dimer results, presumably, from abstraction of hydrogen via a six-membered transition state by the alkoxyl radical initially formed, followed by NO quench of the resultant carbon radical and subsequent dimerization. The nitrosoheptane products result from reaction of solvent with the alkoxyl or carbon radical. The workers showed by equilibration of pure components that the product mixture obtained in the photolysis reaction approximated the equilibrium mixture. All products were shown to be stable under the reaction conditions.

It proved to be possible to trap the alkoxyl radical with atmospheric oxygen to give 1-octyl nitrate as the major product in 60% yield. The yield of nitrate was found to be independent of the concentration of the starting nitrite over the range 0.008-0.318 M. A quantum yield of 0.76 was measured for the disappearance of the nitrite. A quantum of less than unity and the lack of a concentration effect argues strongly against a radical chain mechanism. Since quantum yields of 0.97-0.99 have been measured for the vapor phase photolysis of *t*-butyl nitrite,⁸ it seems reasonable that the observation of a quantum yield of less than unity for solution photolysis of 1-octyl nitrite can be accounted for in terms of reversal of the initial photolytic homolysis reaction.



Kabasakalian and Townley observed that lowering the temperature to -55° decreased the yield of nitrate to less than half its value at 18°, while raising the temperature to 60° gave a slight decrease in yield. Apparently, at lower temperature, unknown side reactions occur to a significant extent and result in lowering of the yield.

Studies of the photolysis of other primary, secondary, and tertiary alkyl nitrites¹⁰ indicate that, when several intramolecular reaction products are equally probable on steric grounds, the one actually observed is the one formed by preferential abstraction of the more labile hydrogen, as expected. Thus, the order of abstraction ease is tertiary>secondary>primary. For example, 2-methyl-2-pentyl nitrite, where a six-membered transition state requires abstraction of a primary hydrogen, gives no products of intramolecular abstraction. The isolated products are, instead, nitrosopropane and acetone (formed by radical elimination) and 2-methyl-2-pentanol (formed by hydrogen abstraction from solvent). In contrast to this result, 2-methyl-2-hexyl and 2,5-dimethyl-2-hexyl nitrite, cases in which secondary and tertiary hydrogens, respectively, are to be abstracted by the alkoxyl radical, gave 49 and 39% yields of the expected nitroso dimers.

The above results indicate a strong preference for a six-membered transition state for the hydrogen abstraction process in the Barton reaction. This preference was further demonstrated in studies of the solution photolysis of aromatic alkyl nitrites by Kabasakalian, Townley, and Yudis.⁹ Irradiation of 5-phenyl-1-pentyl nitrite in benzene solution gave as the only intramolecular reaction product 4-nitroso-5-phenyl-1-pentanol dimer. 3-Phenyl-1-propyl nitrite, when photolyzed under the same conditions, gave no nitroso dimer at all. These results emphasize the importance of the six-membered transition state, since reaction through seven and five-membered transition states would lead to abstraction of a benzylic hydrogen, a thermodynamically more favorable process.

Finally, it is of interest to note that cyclohexyl nitrite, upon photolysis in benzene, gave only a 2% yield of nitroso dimer, while a 29:71 cis:trans mixture of the isomers of 2-ethyl-1-cyclohexyl nitrite gave, under the same conditions, a 33% yield of nitroso dimer.¹¹ These results can be rationalized in terms of the ring conformation necessary for hydrogen abstraction. Cyclohexoxyl radical must abstract hydrogen through the unstable boat form (Figure 1a), while both the cis and trans-2-ethyl derivative can react through the energetically more favorable chair conformation (1b and c). One reason for the success of the Barton reaction in steroid synthesis is that the rings are conformationally locked in the chair form with the angular methyls and hydroxy groups in the favorable 1,3-diaxial configuration.

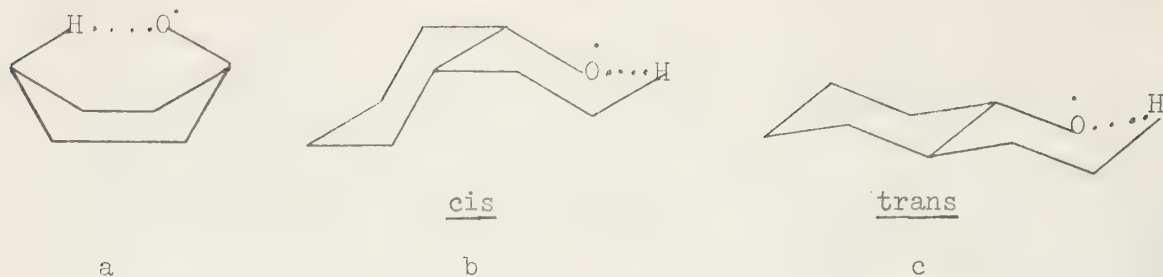
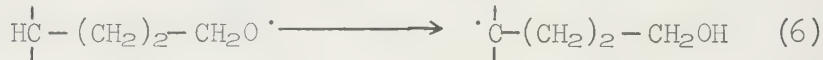
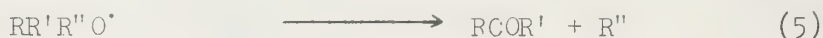
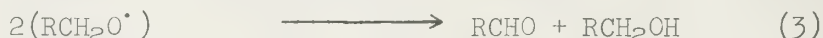
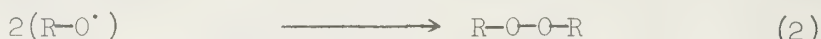


Figure 1

Competing Processes

As has been intimated earlier, the yield of nitroso dimer or oxime from the Barton reaction is kinetically controlled and depends on the relative rates of other competing processes in solution. It is useful, then, to consider these processes individually and determine the best ways to control their rates relative to intramolecular hydrogen abstraction.

Since the alkoxyl radical is the least stable radical involved in the Barton reaction (calculated $\Delta H = -8.5$ kcal/mole for the intramolecular hydrogen abstraction¹³), the reactions which compete with the Barton reaction are those by which alkoxyl radicals achieve stability. It is generally accepted that this occurs in one or more of the following ways: association (1), dimerization (2), disproportionation (3), intermolecular hydrogen abstraction (4), α -cleavage (5), and intramolecular hydrogen abstraction (6).



The thermochemistry of these processes has been extensively reviewed.¹³ Dimerization (2) has never been observed in the photolysis of organic nitrites, probably due to the instability of the resultant peroxide under the reaction conditions. Intramolecular hydrogen abstraction (6) is the key step in the Barton reaction itself. The other pathways will be considered in turn.

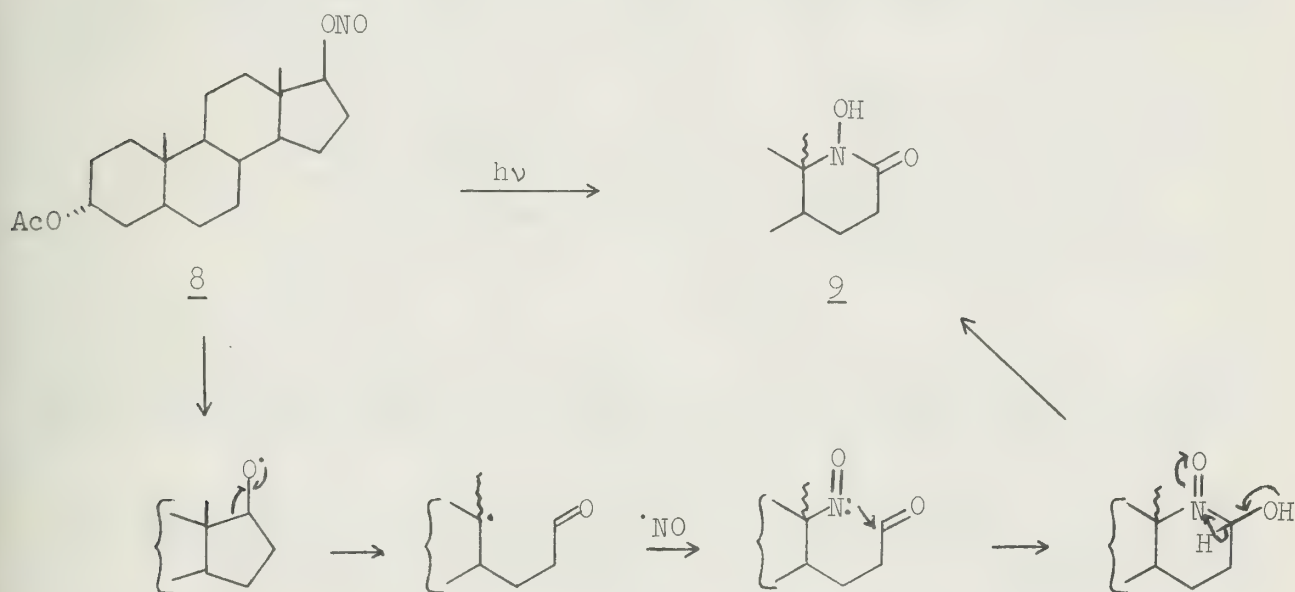
Association with radicals is a common mode of reaction for alkoxyl radicals. This process is apparently responsible for the usual observed quantum yields of 0.1-0.7 for the photolysis of nitrites, where association with NO is relatively rapid. This has been used to synthetic advantage. Akhtar found that irradiation of an alcohol in the presence of a two-fold excess of *t*-butyl nitrite gave "good" yields of an otherwise difficultly prepared nitrite.¹⁴ Association is seldom a problem in synthesis, since it results simply in a lowered quantum yield for the photolysis.

Disproportionation (3) is usually a major side reaction in the photolysis of organic nitrites. In the photolysis of 1-octyl nitrite discussed earlier,⁷ 1-octanal and 1-octanol were formed in 25 and 15% yields, respectively. The

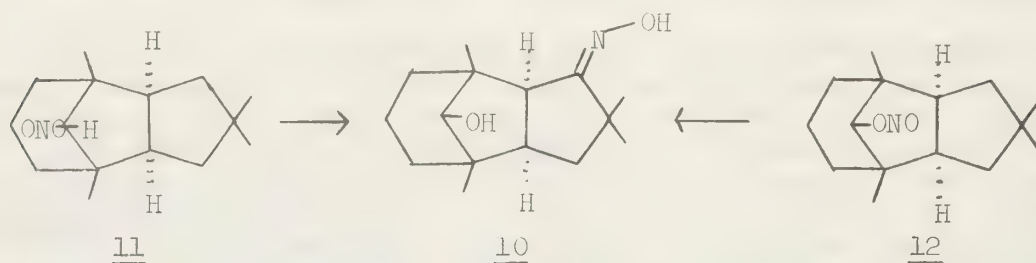
difference in these numbers can be attributed to abstraction of hydrogen from the heptane solvent (process 4) to form the excess 1-octanol. Disproportionation is essentially the only side reaction in the photolysis of primary and secondary nitrites capable of undergoing the Barton reaction and tends to remain a fairly constant portion of the yield in the absence of extraordinary factors favoring Barton reaction or α -cleavage.

As mentioned above, intermolecular hydrogen abstraction does lead to formation of some alcohol from the starting nitrite. With substrates capable of undergoing the Barton reaction or a rapid α -cleavage, this is usually a very minor mode of reaction for the alkoxyl radical. In practice, the solvent is generally found to be the only species transferring hydrogen to the alkoxyl. The yield of solvent products can be minimized by the proper choice of a solvent which itself forms poorly stabilized radicals. Based on the photolysis of 3-phenyl-1-propyl nitrite, Kabasakalian, Townley, and Yudis¹⁰ found that benzene gave the smallest amount of solvent products followed by Freon 113 ($\text{CCl}_3\text{F}-\text{CF}_3\text{Cl}$), acetonitrile, toluene, and heptane in that order.

The number of reports of α -cleavage in attempted Barton reactions is legion and, in the steroid field, these cleavages provide some of the most interesting chemistry. In general, whenever a stabilized radical fragment can be formed by α -cleavage, the cleavage will become a major, if not dominant, mode of reaction. In the photolysis of alkyl nitrites, α -cleavage becomes more prevalent as the length of the carbon chain of the expelled fragment increases. Thus, photolysis of 3-pentyl nitrite in heptane¹⁰ gives nitrosoethane dimer in 5% yield, while photolysis of 4-heptyl nitrite gives nitrosopropane dimer in 8% yield. 2-Methyl-2-pentyl nitrite gives nitrosopropane dimer in 45% yield. α -Cleavage seems to be greatly accelerated by strain in ring systems. Photolysis of cyclopropyl and cyclopentyl nitrites results exclusively in ring fission by this cleavage.¹⁶ An example of this with interesting consequences is provided by the photolysis of the steroidal 17-nitrite 8 which gave the hydroxamic acid 9 via α -cleavage and subsequent rearrangement.¹⁷



The α -cleavage is reversible and, since the alkoxy carbon becomes trigonal during the reaction, reversible α -cleavage can lead to epimerization at that center. An interesting example of this sort of epimerization is provided by the Barton reaction of the nitrites of α -caryophyllene alcohol 11 and its epimer 12. Photolysis of these nitrites gave the same product 10.¹⁸



Finally, numerous examples of α -cleavage in steroidal systems having vinylic or benzylic unsaturation β to the alkoxy or α -ketals glycols, or ketones are known.⁶

Despite the presence of these side reactions, the Barton reaction has found numerous applications in steroid and natural product synthesis since, in these cases, a 15-40% yield in one step by partial synthesis is greatly preferable to a 1% yield by total synthesis. Since the product distribution is largely kinetically controlled and is affected by subtle structural changes, it has generally proved possible to obtain acceptable yields from almost any system by intelligent design of structure and choice of reaction conditions.

Applications

The applications of the Barton reaction in steroid and natural product synthesis are numerous and have been reviewed.^{2,6,14,19,20} Its main use has been for the introduction of functionalization into the otherwise inaccessible angular methyl groups. The rigid structure of steroids is well suited to this purpose. Inspection of molecular models indicates that C-18 can be attacked by an alkoxy radical at C-20, C-8, C-15, or C-11 and C-19 from a radical at C-11, C-6, C-4, or C-2 (Figure 2). In addition, the Barton

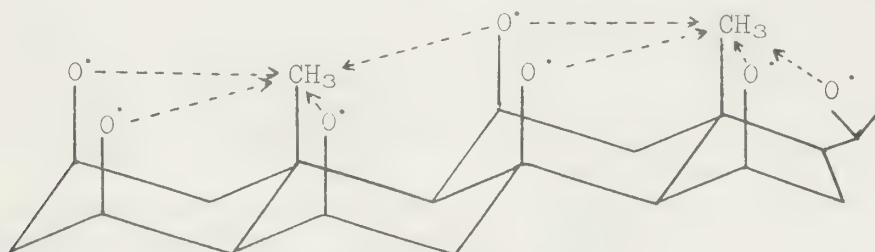
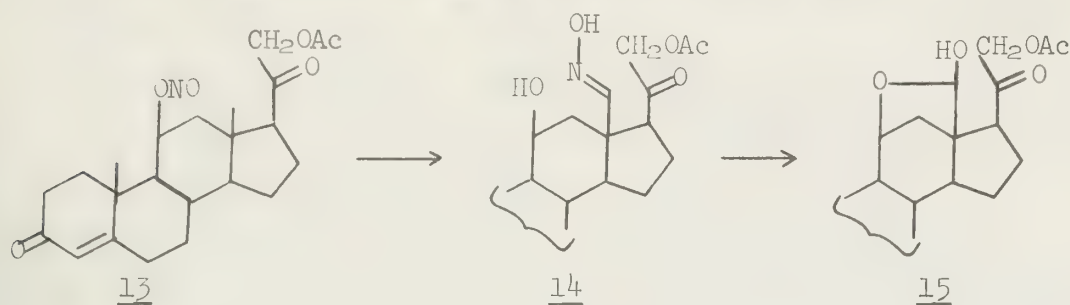


Figure 2

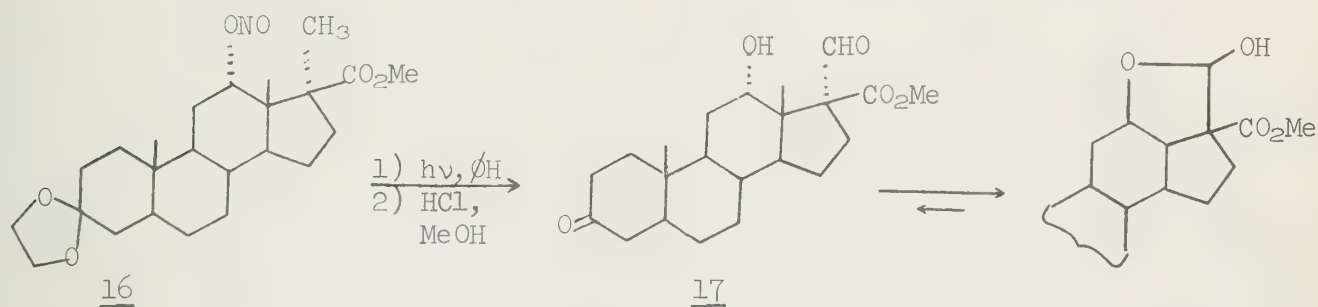
reaction has been useful in the functionalization of suitably disposed ring methylenes. Measurements on Dreiding models indicate an optimum C-O distance of 2-2.7 Å for the hydrogen abstraction.¹⁵

The first application of the Barton reaction was to the synthesis of aldosterone acetate.²¹ Aldosterone is an important salt retention hormone of the adrenal cortex and, prior to 1960, had only been obtained in low yield by total synthesis. The synthesis by Barton and Beaton was one of three initial

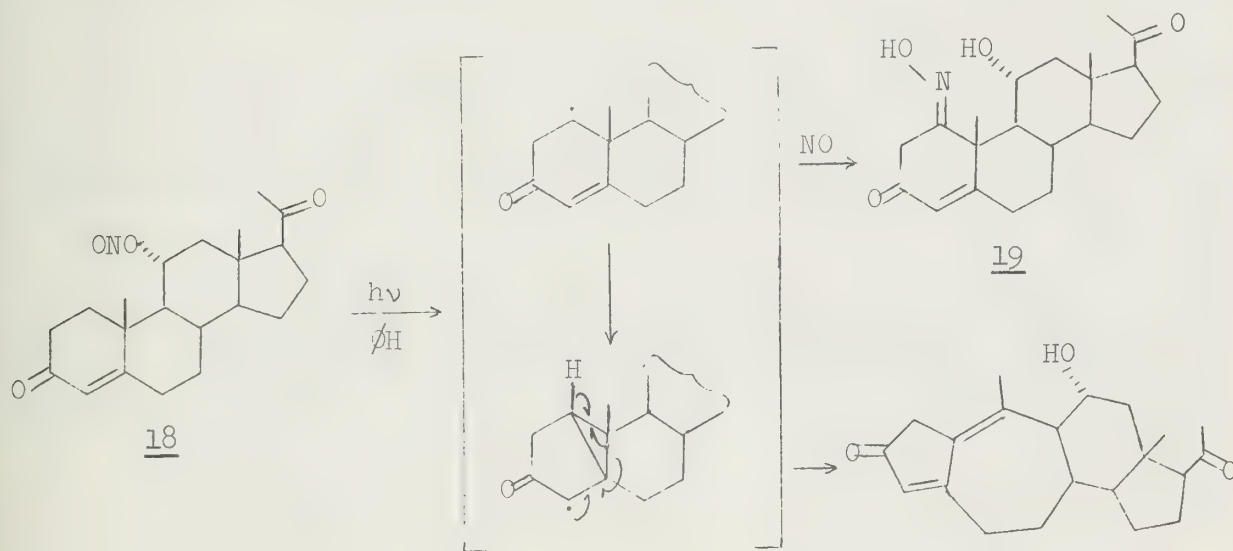
partial syntheses which appeared at about the same time (both of the others employed heteroradical intramolecular hydrogen abstraction as the key reaction). Photolysis in toluene of the 11- β nitrite of corticosterone acetate 13 afforded aldosterone acetate oxime 14 in 21% yield. Treatment of the oxime with nitrous acid gave aldosterone acetate 15 in 15% overall yield from the corticosteroid.



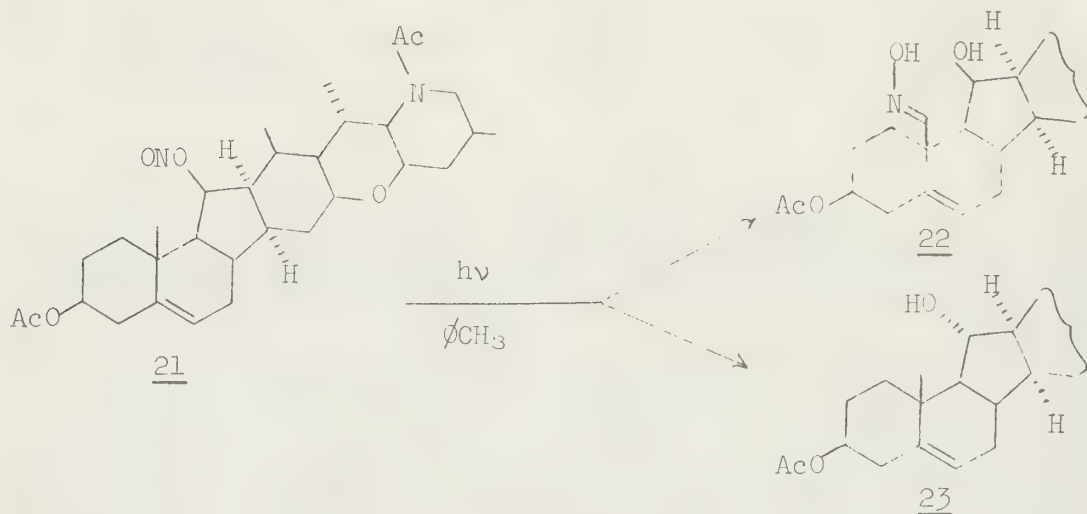
Engel and coworkers have reported²² the functionalization of the 17- α methyl group in an androstane derivative. The nitrite 16 when photolyzed in benzene, followed by hydrolysis of the resultant nitroso dimer with methanolic HCl gave the aldehyde 17.



Riemann and Sarre have reported a novel synthesis of A-nor-B-homosteroids using the Barton reaction.²⁶ Photolysis of the nitrite 18 in toluene yielded two products -- the 1-oximino derivative 19 and the A-nor-B-homo compound 20. The oxime results from NO trapping of the C-1 radical formed by intramolecular hydrogen abstraction, while the other product results from the indicated radical rearrangement.



Finally, Suginome and coworkers²³ have reported an application of the Barton reaction to the synthesis of the jervine derivative 22. Photolysis of the nitrite 21 in toluene gave the oxime 22 in 13% yield. The epimeric alcohol 23 was formed in 31% yield, apparently by reversible α -cleavage.



BIBLIOGRAPHY

1. (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, J. Am. Chem. Soc., 82, 2640 (1960); (b) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, J. Am. Chem. Soc., 83, 4076 (1961).
2. K. Heusler and J. Kalvoda, Angew. Chem. Int. Ed. in Eng., 3 525 (1964).
3. D. H. R. Barton and A. J. L. Beckwith, Proc. Chem. Soc., 335 (1963).
4. L. P. Kuhn, G. C. Kleinspehn, and A. C. Duckworth, J. Am. Chem. Soc., 89, 3858 (1965).
5. J. S. Mills, J. Chem. Soc.(C), 2261 (1966).
6. R. H. Hesse, Advan. Free Rad. Chem., 3, 83 (1969).
7. P. Kabasakalian and E. R. Townley, J. Am. Chem. Soc., 84, 2711 (1962).
8. G. R. McMillan, J. Am. Chem. Soc., 84, 4007 (1962).
9. P. Kabasakalian and E. R. Townley, J. Am. Chem. Soc., 84, 2716 (1962).
10. Ibid., 2718.
11. Ibid., 2724.
12. M. Akhtar and M. M. Pechet, J. Am. Chem. Soc., 86, 265 (1963).
13. P. Gray and A. Williams, Chem. Revs., 59, 239 (1959).
14. M. Akhtar in Advances in Photochemistry, Vol. 2, W. A. Noyes, G. S. Hammond, and J. N. Pitts, eds., Interscience, New York, 1964.
15. D. H. R. Barton, A. J. L. Beckwith, and A. Goosen, J. Chem. Soc., 181 (1965).

16. P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, 27, 2918 (1962).
17. C. H. Robinson, *et al.*, *J. Am. Chem. Soc.*, 83, 1771 (1961).
18. A. Nickon, *et al.*, *J. Am. Chem. Soc.*, 86, 1437 (1964).
19. A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, 17, 1437 (1964).
20. J. M. Erickson and D. L. Forbes in C. Djerassi, *Steroid Reactions*, Holden-Day, San Francisco, 1963.
21. D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, 83, 4083 (1961).
22. C. R. Engel, D. Mukjerhee, and G. J. Beaudoin, *Steroids*, 857 (1973).
23. H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Lett.*, 1557 (1967).
24. D. H. R. Barton and J. R. Hanson, *Chem. Comm.*, 117 (1965).
25. J. R. Hanson, *Tetrahedron*, 22, 1701 (1966).
26. H. Riemann and O. Z. Sarre, *Can. J. Chem.*, 49, 344 (1971).
27. M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, 86, 1528 (1964).
28. M. Akhtar, D. H. R. Barton, and P. G. Sammes, *J. Am. Chem. Soc.*, 87, 4601 (1965).
29. M. Akhtar, D. H. R. Barton, J. M. Beaton, and A. G. Hortmann, *J. Am. Chem. Soc.*, 85, 1512 (1963).
30. D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, 84, 199 (1962).
31. E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, 80, 6686 (1958).
32. R. A. Sneen and N. P. Matheny, *J. Am. Chem. Soc.*, 87, 5503 (1965).

IMINOPHOSPHORANES: PRECURSORS TO NITROGEN HETEROCYCLES

Reported by Ronald L. Amey

November 24, 1975

INTRODUCTION

Iminophosphoranes, also known as phosphinimines or as phosphinimides, were first discovered in 1919 by Staudinger and Meyer.¹ These compounds, of general structure 1, have since been used as synthetic precursors leading

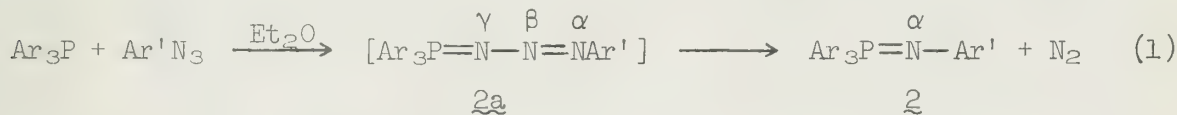


to a variety of products, including substituted ureas,² amines,³ carbodiimides,⁴ and isocyanates.⁴ Because of their synthetic usefulness, iminophosphoranes have been the subject of a large number of reviews.⁵ One of their most interesting aspects has been their use in the formation of various heterocyclic species. Although aziridines,⁶ pyrazines⁷ and related compounds have been prepared, this review will discuss only the preparation of five-membered nitrogen heterocycles from iminophosphorane reagents. General methods of the preparation of these reagents as well as their properties will be discussed.

PREPARATION OF IMINOPHOSPHORANES

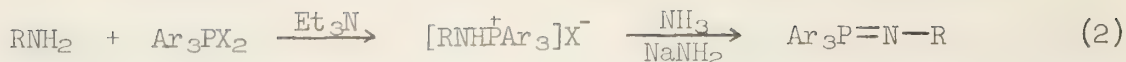
Following the initial work by Staudinger,¹ later workers generated a wide variety of methods for preparation of the iminophosphoranes. Only four of the procedures are sufficiently generalized as to see widespread usage. These methods are: 1) Reaction of trialkyl or triarylphosphines with organic azides; 2) Reaction of triaryldihalophosphoranes with primary amines; 3) Reaction of alkylidenephosphoranes with Schiff bases or organic azides and 4) Desilylation of N-silyliminophosphoranes.

In 1919, Staudinger¹ discovered that tertiary phosphines react with aryl azides to generate N-aryliminophosphoranes and nitrogen. This reaction is the one most commonly used for the preparation of N-aryl substituted compounds. The general reaction scheme (eq. 1), involves the formation of an initial N-P adduct by attack of the phosphine onto the azide nitrogen. Although the



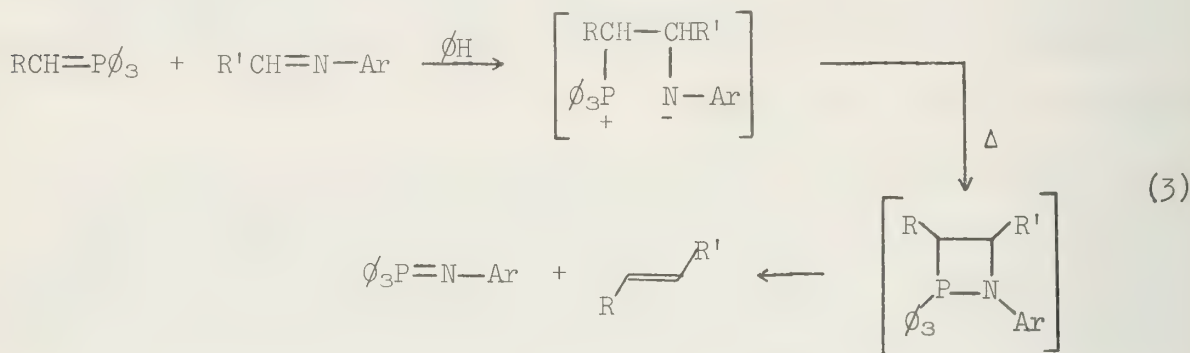
adduct, 2a, is isolable for a few stabilized systems, its decomposition is usually extremely rapid.⁸ The structure of the phosphazide or Staudinger adduct was later confirmed by infrared studies on ¹⁵N-labeled phosphoranes prepared by Bock and Schnöller,⁹ who suggested that the γ and β nitrogen atoms were lost exclusively during thermolysis in solution.

The second method of preparation, the reaction of the triaryldihalophosphoranes with primary amines in base was first described by Horner and Oediger.¹⁰ The phosphoranes are prepared in the presence of triethylamine, followed by deprotonation of the intermediate salt with sodamide-liquid ammonia, although the latter may be treated with triethylamine when aryl substituents are present (eq. 2). Precursor halo salts are generated by

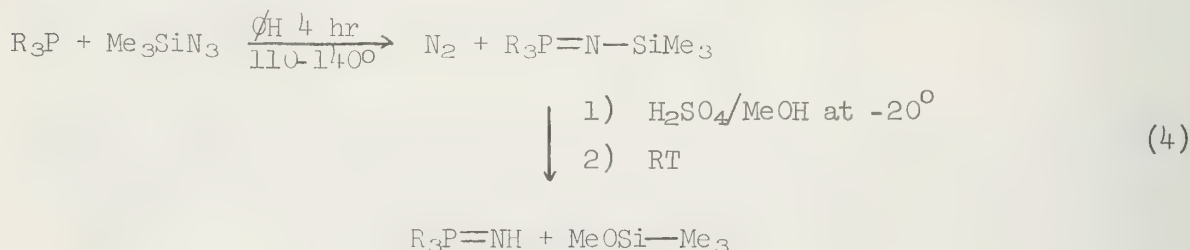


reaction of tertiary phosphines with bromine, chlorine or cyanogen bromide in carbon tetrachloride and do not require isolation but may be used in situ. Zimmer¹¹ later prepared related N-alkyl species by the use of the sodamide reagent. Several alkyl species were prepared by equation 3 in yields exceeding 93%. The versatility of the method is enhanced by the fact that the amine may be replaced by 1,1-disubstituted hydrazines, etc.¹²

Triarylalkylidenephosphoranes (Wittig reagents) are known to react with Schiff bases or with azides to generate N-aryliminophosphoranes and olefins or imines, respectively.¹³ Either route provides ready access to the desired phosphorane, but each is generally restricted to N-aryl substituents. A mechanism for the Schiff base reaction was later proposed (eq. 3).¹⁴ It was later shown that this sequence was not restricted to aryl substituents on the alkylidene portion (R) of the starting phosphorane, but could include ester and amide groups as well.¹⁵



The final mode of iminophosphorane synthesis is the desilylation method, which is the only generally applicable method for the synthesis of the species $\text{R}_3\text{P}=\text{NH}$.¹⁶ After an initial condensation of the tertiary phosphine with trimethylsilyl azide, the N-silyliminophosphorane, which need not be isolated, is treated with a sulfuric acid-methanol mixture at -20° and warmed to room temperature to effect desilylation (eq. 4). Yields for this very facile reaction, which is only limited by the availability of the precursor phosphines, have been reported in the range of 85-95%.^{16,17,18}



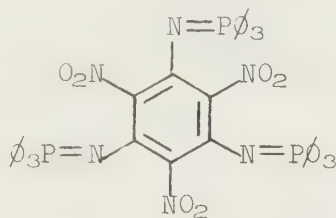
PROPERTIES OF IMINOPHOSPHORANES

Although these compounds have been known for many years, very few data are available on the structure or bonding of the iminophosphoranes, since ^{31}P -NMR and X-ray studies are scarce for this class.

It is generally considered that the geometry about the phosphorus atom is similar to that in alkylidenephosphoranes, i.e., tetrahedral.¹⁹ The

overlap of a vacant 3d-orbital on phosphorus with the filled p-orbital on nitrogen is considered to lead to a $p\pi d\pi$ interaction which increases the bond strength relative to a P-N single bond.

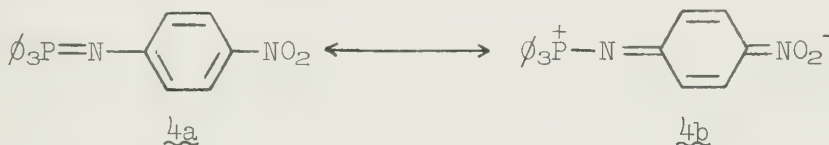
X-Ray crystallographic data which have been gathered for compound 3, show P=N bond lengths (1.54 Å) to be considerably shortened relative to P-N



3

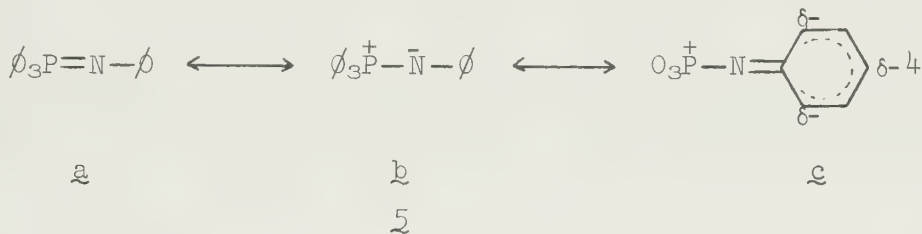
single bonds and the C-N-P angle to be enlarged (137°) relative to that expected for an sp^2 hybrid (120°).²⁰ Such differences were attributed by the authors to $p\pi d\pi$ interactions between nitrogen and phosphorus, although such bond contraction might also be explained in terms of an ylid structure.

Recent infrared studies on ^{15}N -labeled species indicate that most P-N bond stretching frequencies lie between 1140 and 1370 cm^{-1} .²¹ For N-aryl substituents, it was found that groups which increase contributions of the type shown in 4b increase the P=N bond stretching frequency, ν .^{21b} A change



of the para substituent from $\text{R} = -\text{N}(\text{Et})_2$ to $\text{R} = -\text{NO}_2$ shifts ν from 1328 cm^{-1} to 1373 cm^{-1} .^{21b}

The use of ^{13}C -NMR in the study of iminophosphoranes has been limited to work done on compound 5. The fact that carbon-4 is shielded by 4.5 ppm



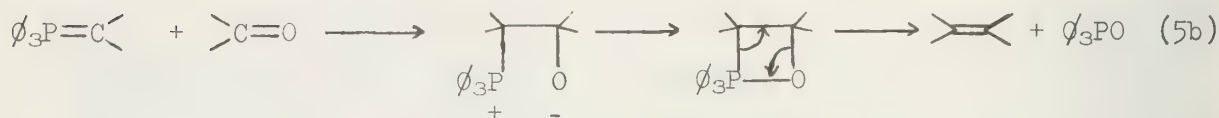
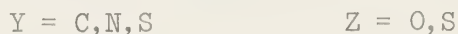
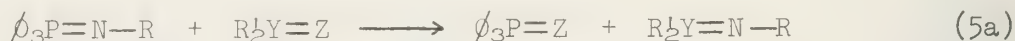
(+117.3 ppm) in 5 relative to the analogous carbon in a related phosphonium salt ($\phi_3\text{P}^+\text{NH}\phi\text{Br}^-$, +121.8 ppm), suggests that 5a is only a minor contributor to the total structure of 5.²²

Dipole moment data show that the P-N bond moment (μ) is directed from phosphorus to nitrogen and is not reversed in the presence of highly electronegative groups on phosphorus.²³ The fact that the P=N bond moment ($\mu = 4.21$ D, $\phi_3\text{P}=\text{NH}$) is nearly the same as that of the P=O ($\mu = 4.28$ D, $\phi_3\text{P}=\text{O}$) indicates that the P=N bond polarity is greater than that of the P=O bond polarity. Thus, the ylid character of the iminophosphoranes is expected to play a sizable role in determining their reactivity.

PREPARATION OF HETEROCYCLIC SPECIES

Iminophosphoranes are the nitrogen analogs of the alkylidenephosphoranes (Wittig reagents), both structurally and in terms of their reactivity, which is characterized by a basic and nucleophilic nitrogen atom in a compound often described as a phosphorus-nitrogen ylid.

Thus, the generally applicable reaction of iminophosphoranes shown in eq. 5a is the direct nitrogen analog of the reaction of an alkylidene-phosphorane (Wittig reagent) with a carbonyl compound to generate olefins (eq. 5b).^{5a, 5d, 19}

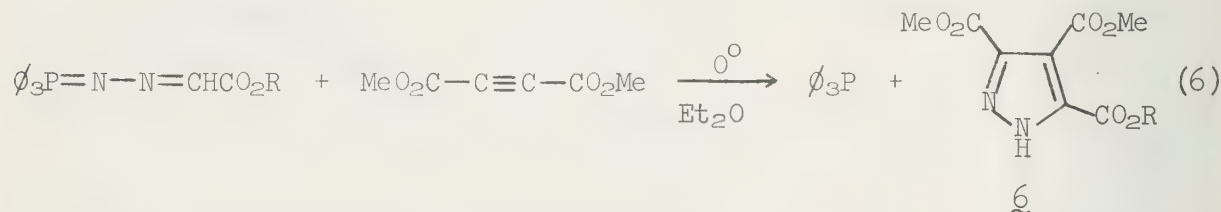


Other condensations which both types of phosphoranes undergo include reactions with carbon dioxide, isocyanates and ketenes.

In all cases, the by-product generated is either triphenylphosphine oxide or sulfide. It appears that the formation of the thermodynamically stable P=O or P=S bond acts as a driving force for completion of the reaction.

In the following examples, the general reaction shown in eq. 5a has been applied to the generation of a series of heterocyclic species containing nitrogen in a five-membered ring. The species to be considered are the pyrazoles, oxazoles, oxadiazoles and tetrazoles.

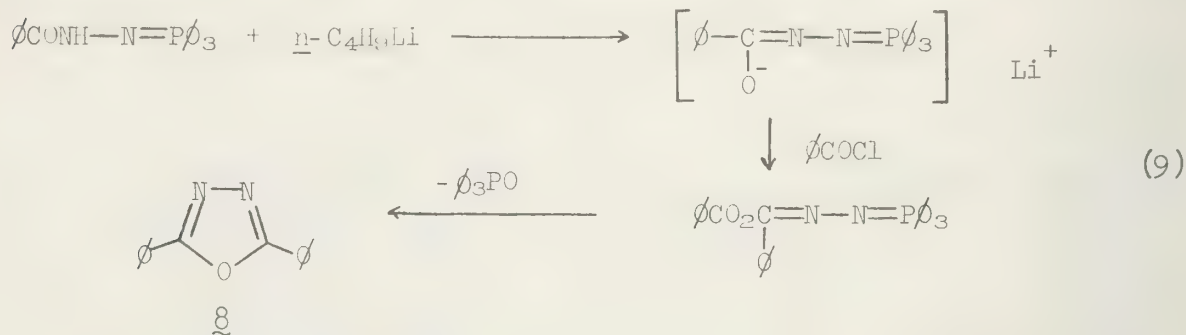
The use of iminophosphoranes to generate substituted pyrazoles has received modest attention and is probably the least generalized and studied of the syntheses to be discussed. In fact, initial synthesis of **6** involves a substituted iminophosphorane better described as a phosphazine (prepared from triphenylphosphine and a diazo compound). This work in 1964 led to pyrazole formation as shown (eq. 6).²⁵



In a related series of reactions, Plieninger and vor der Brück²⁶ generated 3,4,5-trisubstituted pyrazoles in high yield. The most comprehensive work on pyrazole syntheses has been that of Schweizer, *et al.*²⁷ The latter found that reaction of an *N*-substituted phosphorane with a triarylalkyl-phosphonium salt generated a mixed salt containing an imino function. This compound was converted to a bis-alkylidenephosphorane and then was cyclized to the pyrazole (eq 7.)

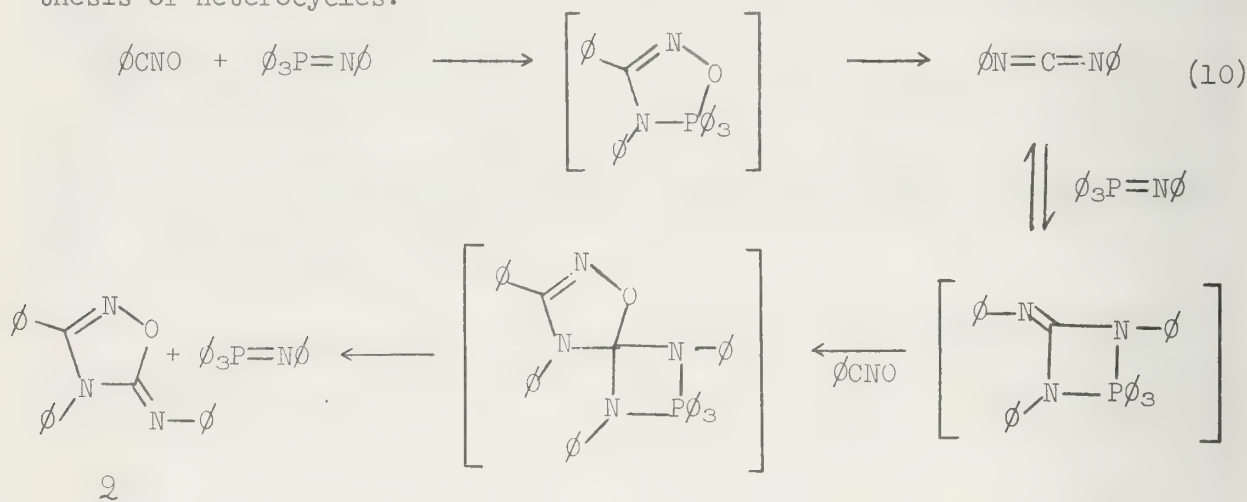
generation of the intermediate reactants, are only 40-50%, which is comparable with the overall yields from iminophosphoranes. The latter method is highly competitive with the Robinson synthesis and is often more facile, cheaper and easily accessed than the Robinson synthesis itself.

The earliest report of iminophosphorane synthesis of the 2,5-disubstituted 1,3,4-oxadiazoles, **8**, was in 1968.³⁴ After the preparation of the iminophosphorane precursor by a standard procedure,¹⁴ the authors generated its lithium salt, which was subsequently treated with an acid chloride and then cyclized to the oxadiazole, **8** (eq. 9). A variety of substituents was tested



in the 2- and 5- positions and found to give high yields (60-90%) under very mild reaction conditions (stirring for 24 hr at 25° in ether solution).

Huisgen and Wulff³⁵ reported the formation of the *N*-phenylanil of **2**, by the reaction of *N*-phenyltriphenyliminophosphorane with benzonitrile oxide in ether (eq. 10). The resultant ketone from the anil was obtained in 22% yield, which shows another unique application of the iminophosphorane synthesis of heterocycles.



Of the other routes available to oxadiazoles, the only one capable of achieving comparable yields with the same substituents is the modified method of Stolle.³⁶ This involves a dehydration of a symmetric diacylhydrazine at elevated temperatures to give desired products in yields of 80-90%. Although it gives yields and substitution patterns which are comparable to the phosphorane synthesis, the method of Stolle is much harsher and reaction conditions are much more vigorous, using H₂SO₄·SO₃, P₂O₅, etc., at elevated temperatures.

8. G. Wittig, K. Schwarzenbach, Justus Liebigs Ann. Chem., 650, 1 (1961).
9. H. Bock, M. Schnöller, Chem. Ber., 102, 138 (1969).
10. L. Horner, H. Oediger, Justus Liebigs Ann. Chem., 627, 142 (1959).
11. H. Zimmer, G. Singh, J. Org. Chem., 28, 483 (1963).
12. H. Zimmer, G. Singh, J. Org. Chem., 29, 1579 (1964).
13. H. Hoffmann, Chem. Ber., 95, 2563 (1962).
14. H. J. Bestmann, F. Seng, Tetrahedron, 21, 1373 (1965).
15. G. R. Harvey, Abstracts of Papers, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, No. K051.
16. L. Birkofer, A. Ritter, S. M. Kim, Chem. Ber., 96, 3099 (1963).
17. L. Birkofer, S. M. Kim, Chem. Ber., 97, 2100 (1964).
18. T. W. Rave, H. R. Hays, J. Org. Chem., 31, 2894 (1966).
19. A. W. Johnson, Ylid Chemistry, Academic Press, New York, N. Y., 1966, pp 217-230.
20. (a) T. Cameron, C. Prout, Chem. Commun., 455 (1967); (b) T. Cameron, C. Prout, J. Chem. Soc., C, 2281 (1969).
21. (a) W. Wiegräbe, H. Bock, H. Luttke, Chem. Ber., 99, 3737 (1966); (b) W. Wiegräbe, H. Bock, Chem. Ber., 101, 1414 (1968).
22. T. A. Albright, W. J. Freeman, E. E. Schweizer, J. Am. Chem. Soc., 97, 940 (1975).
23. A. E. Lutskii, L. I. Samarai, L. A. Kochergina, A. V. Shepel, Z. A. Shevchenko, G. I. Derkach, E. S. Kozlov, B. S. Drach, Zh. Obshch. Khim., 37, 2042 (1967); Chem. Abstr., 68, 34387a (1968).
24. G. M. Phillips, J. S. Hunter, L. E. Sutton, J. Chem. Soc., 146 (1945).
25. G. W. Brown, R. C. Cookson, I. D. R. Stevens, Tetrahedron Lett., 1263, (1964).
26. H. Plieninger, D. vor der Brück, Tetrahedron Lett., 4371 (1968).
27. E. E. Schweizer, C. S. Kim, C. S. Labaw, W. P. Murray, J. Chem. Soc., Chem. Commun., 7 (1973).
28. F. N. Hayes, B. S. Rogers, D. G. Ott, J. Am. Chem. Soc., 77, 1850 (1955).
29. R. A. Jeffreys, J. Chem. Soc., 3396 (1967).
30. CIBA Ltd., Belgian Patent 619,755 (1963); Chem. Abstr., 58, 12713 (1963).
31. F. W. Short, L. M. Long, J. Heterocycl. Chem., 6, 707 (1969).
32. E. Zbiral, E. Bauer, J. Stroh, Monatsh. Chem., 102, 168 (1971).
33. R. Robinson, J. Chem. Soc., 95, 2167 (1909).
34. C. C. Walker, H. Shechter, J. Am. Chem. Soc., 90, 5626 (1968).
35. R. Huisgen, J. Wulff, Chem. Ber., 102, 1848 (1969).
36. R. Stolle, J. Prakt. Chem., 60, 145 (1904).
37. E. Zbiral, J. Stroh, Justus Liebigs Ann. Chem., 725, 29 (1969).
38. M. Pailer, E. Haslinger, Monatsh. Chem., 101, 508 (1970).

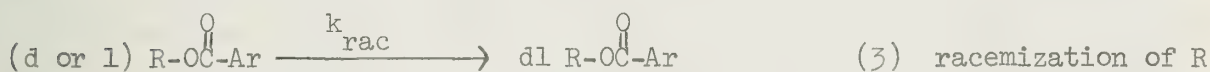
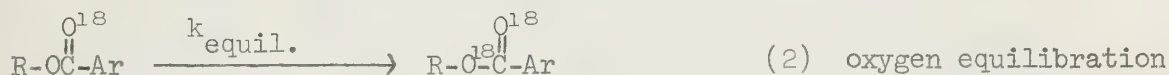
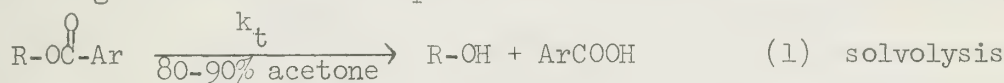
ION PAIRS: STEREOCHEMISTRY OF RETURN AND A NOVEL "S_N2-LIKE"
SUBSTITUTION AT A TERTIARY CARBON

Reported by Gary W. Nickel

December 1, 1975

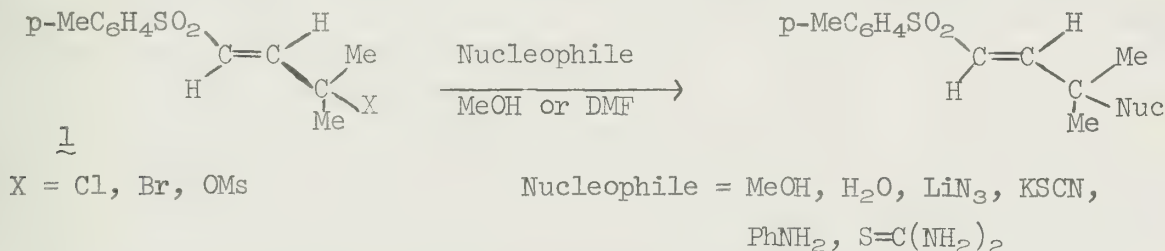
The classical S_N1-S_N2 solvolysis scheme of Ingold,¹ although generally successful, has been insufficient to explain the "borderline" cases of secondary substrates.² It has become apparent that ion pair formation³ (the Winstein Ion Pair Scheme) and nucleophilic solvent assistance⁴ are important factors in many solvolyses.

Goering and coworkers, in some elegant experiments, have studied the stereochemistry of return in a number of resonance-stabilized ion pair systems, notably the benzhydryl,⁵ para-substituted benzhydryl,⁶ 2-phenyl-2-butyl,⁷ α-methyl-γ-phenylallyl,⁸ α-phenylethyl,⁹ and α-p-anisylethyl-p-nitrobenzoates.⁹ These investigations involved comparisons of the rates of reactions 1-3.

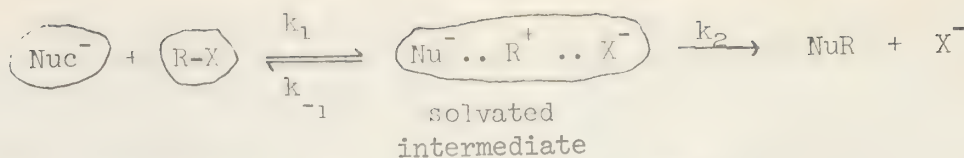


Reaction (1) represents the first order solvolysis, while reactions (2) and (3) are intramolecular first-order transformations of the unsolvolyzed ester which result from ion pair recombination. Providing oxygen equilibration is complete (likely in these resonance stabilized systems), $(k_{\text{eq}} + k_t)$ is the rate constant for total ionization, k_{eq}/k_t is the ratio of return to solvolysis, and $k_{\text{rac}}/k_{\text{eq}}$ is the fraction of return that results in loss of optical configuration. Goering has shown the existence of intimate and solvent-separated ion pairs (trapped by NaN₃),^{6a} and that solvolysis from the solvent separated ion pair may result from backside approach by nucleophile but frontside capture by solvent.^{6b} Evidence also indicates that the attractive forces in ion pairs are weaker the more delocalized is the positive charge, resulting in more extensive equilibration and racemization.^{6b,8}

Bordwell and coworkers observed that compound 1 underwent substitutions, accompanied by only small amounts of elimination, with a variety of weakly basic nucleophiles in both protic and dipolar aprotic solvents with clean second-order kinetics.¹⁰



Compound 1 resembles *t*-BuBr in most mechanistic tests, but resembles *i*-PrBr in its rate and pattern of substitution, and in its sensitivity to solvent and nucleophile participation.¹¹ Bordwell proposed an S_N2¹-ion pair mechanism^{11,12} in which ion pair formation involves nucleophilic assistance to give a solvated ion sandwich intermediate. The rate-determining step is an attack by the nucleophile on the ion pair from within the ion sandwich.



Possible alternative mechanisms such as S_N2' followed by S_N1' , elimination-addition, Michael addition followed by intramolecular displacement, or radical ion formation¹³ were shown to be inoperable.¹⁴ Among the strong circumstantial evidence for an ion-pair mechanism¹⁵ is: (a) increased rate with solvent ionizing power, (b) positive salt effect, (c) $k^{\text{OMs}}/k^{\text{Br}}$ leaving ratio > 1 , (d) substitution by the more electronegative end of ambident nucleophiles (RNCS), (e) large β -deuterium isotope effect.

BIBLIOGRAPHY

1. J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1935).
2. "Solvolytic Substitution in Simple Alkyl Systems" by J. M. Harris in "Progress in Physical Organic Chemistry", Vol. 11, A. Streitwieser, Jr., and R. W. Taft, Ed., 1974, p. 89.
3. (a) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, and G. C. Robinson, *J. Am. Chem. Soc.*, 78, 328 (1956); (b) S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc. Spec. Publ. No. 19*, 109 (1965).
4. (a) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 92, 2538 (1970); (b) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *ibid.*, 92, 2540 (1970); (c) P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *ibid.*, 92, 2542 (1970); (d) D. J. Raber, J. M. Harris, and P. v. R. Schleyer, *ibid.*, 93, 4829 (1971).
5. H. L. Goering and J. F. Levy, *ibid.*, 84, 3853 (1962).
6. (a) H. L. Goering and J. F. Levy, *ibid.*, 86, 120 (1964); (b) H. L. Goering and H. Hopf, *ibid.*, 93, 1224 (1971).
7. H. L. Goering and S. Chang, *Tetrahedron Lett.*, 3607 (1965).
8. H. L. Goering and E. C. Lindsay, *J. Am. Chem. Soc.*, 91, 7435 (1969).
9. H. L. Goering, R. G. Briody, and G. Sandrock, *ibid.*, 92, 7401 (1970).
10. F. G. Bordwell and T. G. Mecca, *ibid.*, 94, 2119 (1972).
11. F. G. Bordwell, P. F. Wiley, and T. G. Mecca, *ibid.*, 97, 132 (1975).
12. For earlier proposals that such a mechanism might exist, see (a) S. Winstein, A. Ledwith, and M. Hojo, *Tetrahedron Lett.*, 341 (1961); (b) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N.Y., 1963, p. 138.
13. N. Kornblum and F. W. Stuchal, *J. Am. Chem. Soc.*, 92, 1804 (1970).
14. F. G. Bordwell and G. A. Pagani, *ibid.*, 97, 118 (1975).
15. (a) F. G. Bordwell and T. G. Mecca, *ibid.*, 97, 123 (1975); (b) F. G. Bordwell and T. G. Mecca, *ibid.*, 97, 127 (1975).

KETENES: VALUABLE INTERMEDIATES IN ORGANIC SYNTHESIS

Reported by William Baker

December 4, 1975

Ketenes, compounds containing the functional group $\text{R} \text{---} \text{C}=\text{C}=\text{O}$,^{1,2,3,4} made their first appearance more than 65 years ago.^{5,6} As highly reactive electrophiles, they are of considerable interest in organic synthesis.

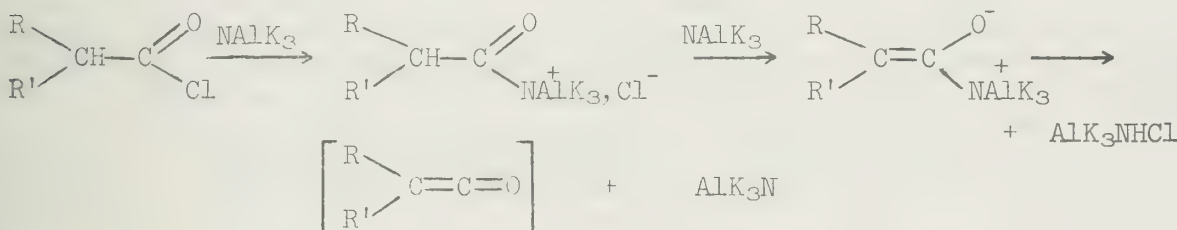
This seminar will deal with three general methods of ketene synthesis; dehydrohalogenation of acid halides, dehalogenation of α -halo acid halides and rearrangement of α -diazoketones. Since ketenes are rarely isolated, their synthetic utility will be discussed under each preparative method. The two *in situ* trapping reactions ketenes undergo are interception by nucleophilic reagents and 2+2 cycloadditions. The scope of the cycloaddition reaction will be discussed in detail. Ketene analogues will be discussed and evidence for both the concerted and dipolar cycloaddition reaction will also be presented.

PREPARATIVE METHODS AND SYNTHETIC APPLICATIONS

A. Dehydrohalogenation of Acid Halides

One of the earliest and most widespread methods for the generation of ketenes *in situ* is the elimination of hydrogen halides from acid halides with a hydrogen atom in the alpha position under the action of strongly basic tertiary amines. The mechanism of this reaction has received much attention. Since it was proved possible to isolate adducts of acid halides with weakly basic tertiary amines (pyridine, N,N-diakylanilines), then by analogy the interaction of more basic tertiary amines involves the formation of a quaternary salt (Scheme I).^{7,8a,b} Another possible mechanism is an E2 bimolecular elimination of HCl.

Scheme I




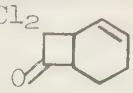

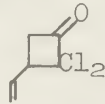
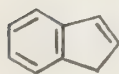
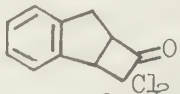

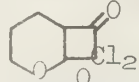



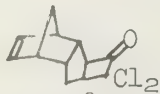

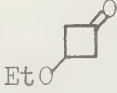



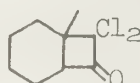

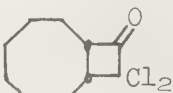


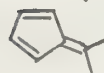
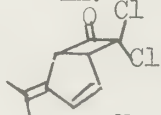

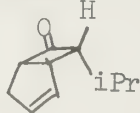
Ketenes may be trapped with various substrates. The most common reaction they undergo is the [2+2] cycloaddition.

The preparation of dichloroketene was independently reported from three laboratories in 1965-1966.^{9a,b,c} It was prepared in the presence of cyclopentadiene and only the 1,2 cycloadduct was produced. Other dihalo-, monohalo-, and aldoketenes (monosubstituted ketenes) have been prepared and trapped with various olefinic substrates (Table I).

Other unsaturated bonds undergo [2+2] cycloadditions. Imines add to dichloroketene in nearly quantitative yield to produce α,α -dichloro- β lactams which are potential precursors of various functionally substituted β -lactams.¹⁵ α,β -Unsaturated imines yield both 1,2- and 1,4-cycloadducts. This is possible in these systems because cycloadditions across the $\text{C}=\text{N}$ is well established to be a two-step process via a dipolar intermediate.^{16a,b,c,d}

One of the most interesting synthetic applications of ketenes has been the conversion of (1) to tropolone (2) in 65% yield by hydrolysis in aqueous acetic acid containing sodium acetate.¹⁷ This transformation has been extended

Table I.

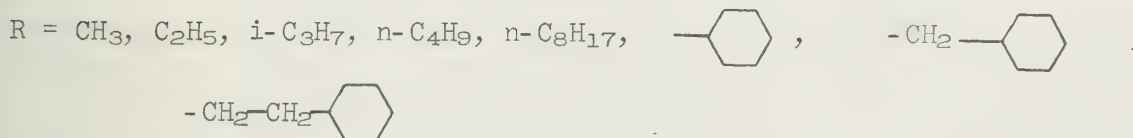
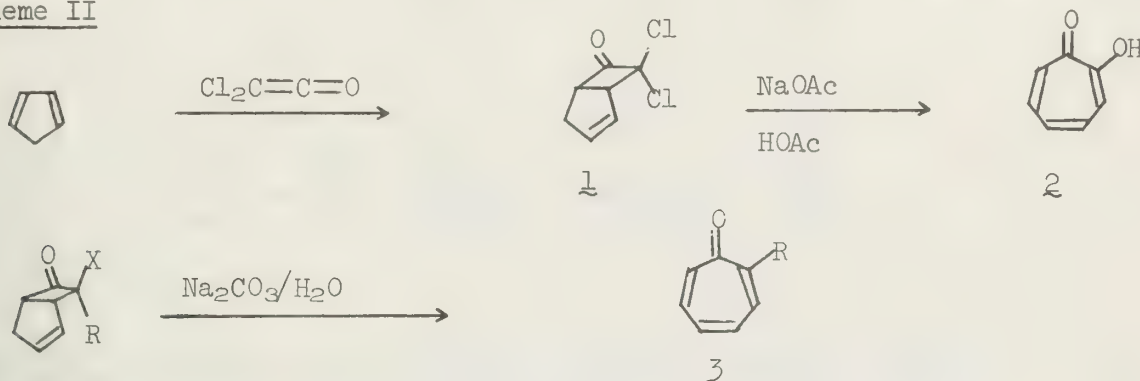
Olefin	Solvent	Ketene ^{*,**}	Product	Yield %
	light pet. ether	$\text{Cl}_2\text{C}=\text{C}=\text{O}^{*,**}$		60 ³
	cyclohexane	$\text{Cl}_2\text{C}=\text{C}=\text{O}^{*,**}$		88 ³
	light pet. ether	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		41 ³
	light pet. ether	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		35 ³
	neat	$\text{Cl}_2\text{C}=\text{C}=\text{O}^{*,**}$		57 ³
	light pet. ether	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		58 ³
	ether	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		45 ¹⁴
	light pet. ether	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		83 ³
	ether	$\text{Cl}_2\text{C}=\text{C}=\text{O}^{**}$		— ¹⁰
	neat	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		50 ¹¹
	neat	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		100 ¹¹
	hexane	$\text{Cl}_2\text{C}=\text{C}=\text{O}^*$		95 ¹²
	CHCl_3	$i\text{-PrHC}=\text{C}=\text{O}^*$		37 ¹³

* Ketene was prepared by dehydrohalogenation of an acid halide with dry triethylamine

** Ketene was prepared by activated zinc dehalogenation of an alpha halo acid halide

to the synthesis of various tropolone derivatives and to the synthesis of tropone from the monochloroketene-cyclopentadiene adduct (Scheme II).¹⁸

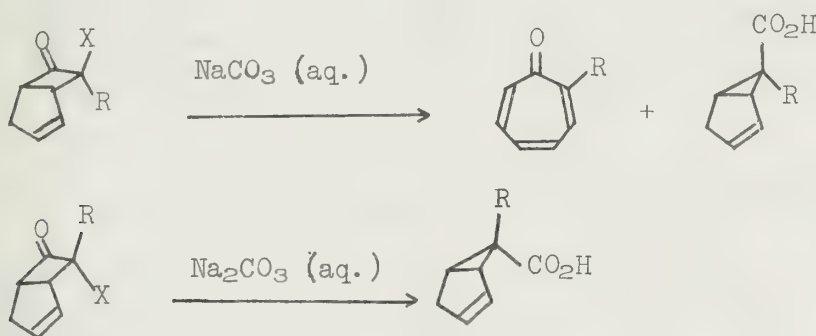
Scheme II



The solvolysis of some alkylhaloketene-cyclopentadiene adducts to produce 2-alkyltropones has been explored (3). The substituted tropones prepared are listed in (Scheme II).^{19,20} It was found that the alkyltropones were produced only from the endo-alkylisomer of the alkylhaloketene-cyclopentadiene adducts. The exo-alkyl adducts gave only a Favorskii type ring contraction (Scheme III). The ring contraction is stereospecific, i.e., the exo-alkylcycloadduct is converted to the exo-alkylcyclopropanoic acid and the endo-alkylcyclobutanone gives only the endo-alkylcyclopropanoic acid.

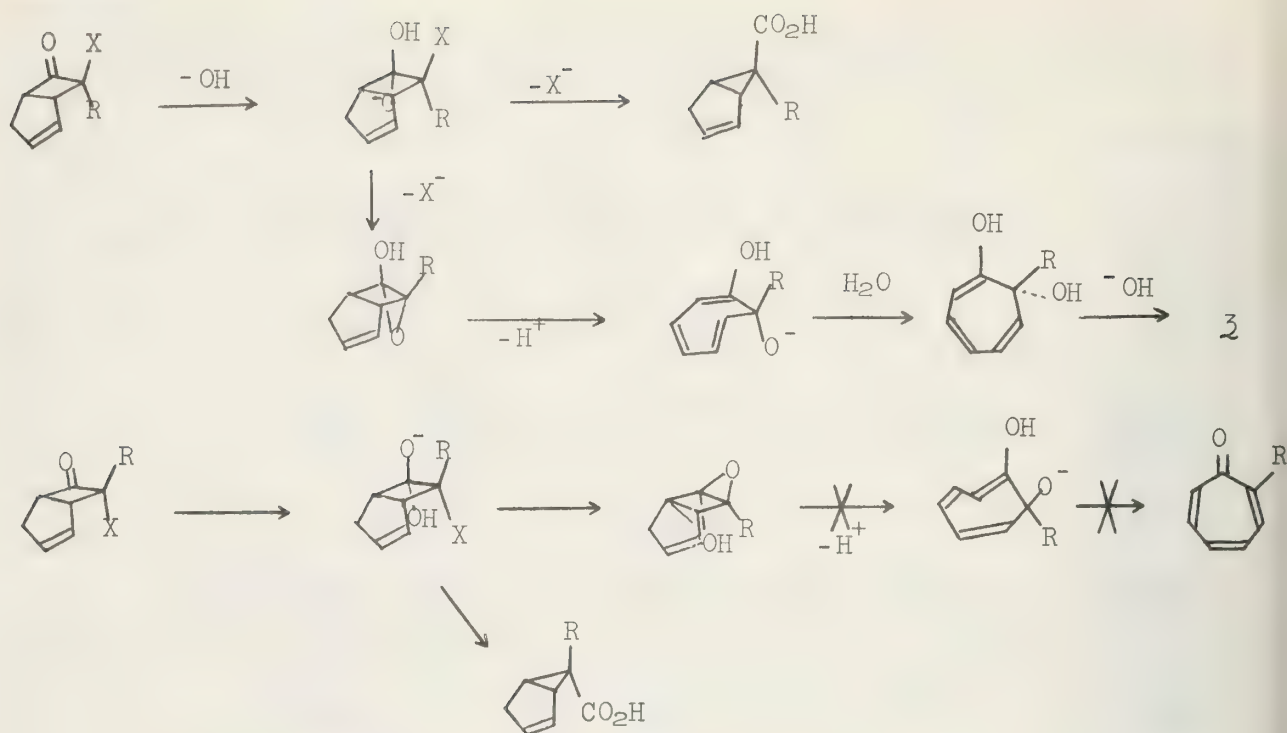
The mechanistic rationale behind these observations are shown in scheme IV. The key step in the tropone formation is a facile disrotatory ring

Scheme III



opening of the endo epoxide (4), thus effecting the desired trans displacement. The opening of the epoxide (5) is severely disfavored, since the resulting disrotatory rotation would lead to a trans olefin in a seven membered ring (6).

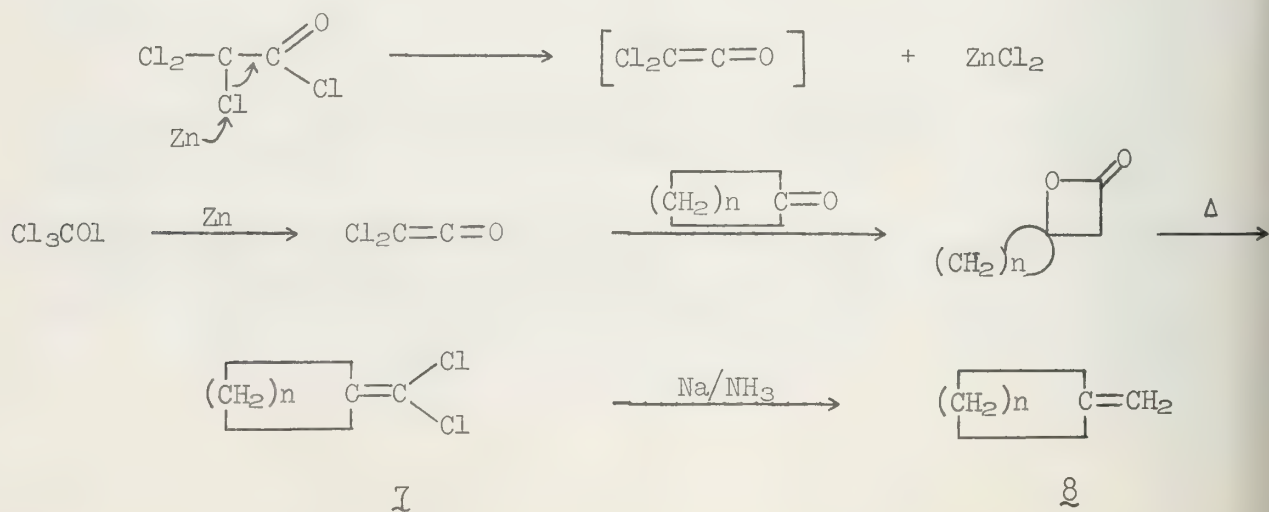
Scheme IV



B. Dehalogenation of α -Halo Acid Halides

A second method of generating ketenes, primarily dihaloketenes, is the dehalogenation with activated zinc of α -halo acid halides. The mechanism is analogous to the debromination of 1,2 dibromides to give olefins. (Scheme V). Generation of dichloroketene by this method is comparable with that of dehydrohalogenation. However zinc dehalogenation is preferred in the cycloaddition of dichloroketene to ketones. Apparently the $\text{Zn}/\text{ZnX}_2 \cdot \text{Et}_2\text{O}$ activates the ketones to cycloaddition. Unfortunately, simple aldehydes do not undergo cycloaddition under these conditions as trimerization and polymerization of the aldehyde occurs. Brady used this method for the preparation of β lactones which are converted to dichloromethylenealkanes (7) and methylenealkanes (8) (Scheme V).^{21,22}

Scheme V

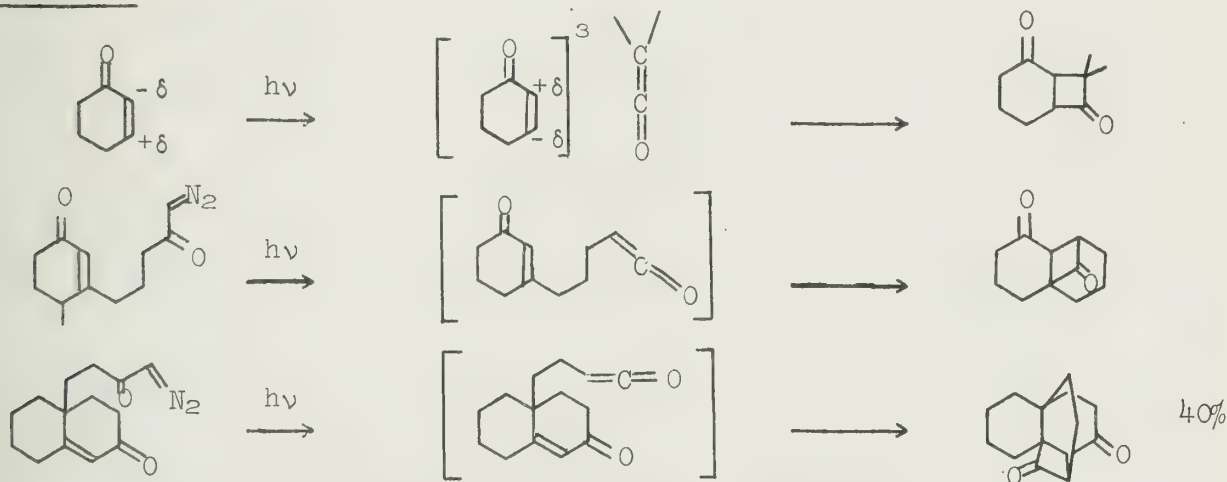


n	Yield% 1	Yield% 2 (from 1)
4	30	80
5	50	90
6	52	90
7	45	85

C. Photolytic and Catalytic Decomposition of α -Diazoketones

The third general method for the preparation of ketenes involves the decomposition of α -diazoketones. They in turn are prepared in good yield from either carboxylic acids or ketones. The Arndt-Eistert synthesis is a procedure for converting a carboxylic acid to its next higher homolog or derivative of the homologous acid. The three steps involved generally can be accomplished in one day with overall yields of 50-80%.²³ An acid is formed in the presence of water, an ester is produced in an alcohol and an amide results when ammonia or an amine is used. Silver oxide is generally used to initiate the rearrangement of the carbene known as the Wolff rearrangement. When the diazoketone is cyclic the Wolff rearrangement gives ring contraction with interception of the ketene.^{24,25} Becker has prepared 1,4-diketones in the presence of excited enones.^{26,27} Normally ketenes are unreactive towards electron deficient olefins. In the excited, triplet state of the enone charge distribution shifts. The β -carbon atom of the excited enone attacks the ketene carbonyl carbon atom (Scheme VI).

Scheme VI



D. Ketene Analogues

A new and potentially useful route for the synthesis of four-membered rings has been developed by Ghosez.²⁸ Tetramethylketeneimmonium fluoroborate adds to olefins and dienes with exceptional ease. The reaction

conditions are mild, the yields are excellent and the starting material is cheap and readily available. 1-Chloro-N,N-2-trimethylpropenylamine (9) is prepared in good yield from N,N-dimethylisobutyramide and phosgene, followed by elimination of HCl with triethylamine. Addition of silver tetrafluoroborate in CH₂Cl₂ at -60 precipitates silver chloride and the immonium salt (10) reacts in situ with olefins or dienes (Scheme VII). Cycloadducts obtained with various olefins and dienes are summarized (Table II).

Scheme VII

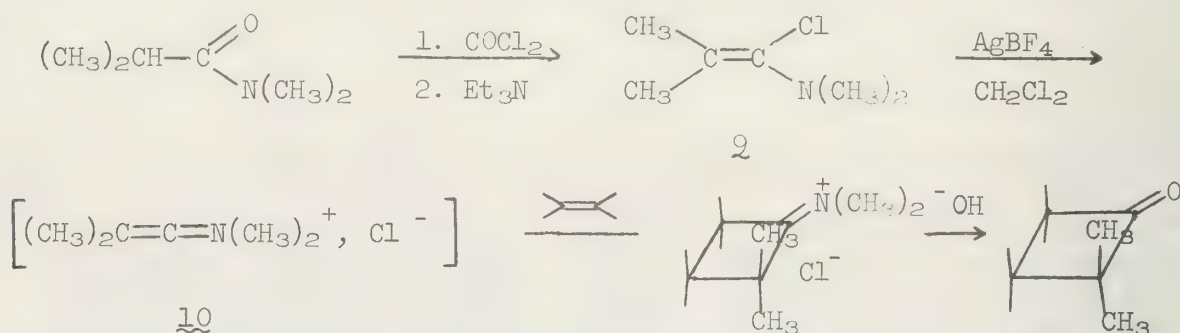


Table II

Substrate	Adduct yield %	Cyclobutanone yield %
Butadiene	84	86
Cis piperylene	85	93
Trans piperylene	82	89
Cyclohexene	83	89
Cis cyclooctene	86	88
Trans cyclooctene	85	87

The keteneimmonium salts show the same regiospecificity in cycloadditions as ketenes themselves. Stereochemistry is also retained in the cis-, trans-cyclooctene cycloadditions. Hydrolysis has been shown to cause epimerization of the adducts. Short reaction times and buffered solutions are used to prevent isomerization.

CONCERTED AND DIPOLAR CYCLOADDITION PROCESSES

Cycloaddition of ketenes to unsaturated bonds can be viewed as proceeding by either a concerted or dipolar mechanism. Kinetic evidence for the concerted mechanism has been presented by Brady and O'Neal.³⁰

The cycloaddition of diphenylketene to dihydropyran was studied. The reaction was first order in diphenylketene and first order in dihydropyran. The second order rate constants at various temperatures and solvents are given in (Table III) and (Table IV). The heat of activation (ΔH^*) was found

Table III Second-Order Rate Constants

Temp. C	$k \times 10^5 \text{ l. mole}^{-1} \text{ sec.}^{-1}$
30	1.65 ± 0.07
40	2.35 ± 0.05
50	4.55 ± 0.14
60	6.62 ± 0.24

Table IV Effects of Solvent on the Second-Order Rate Constant at 40°

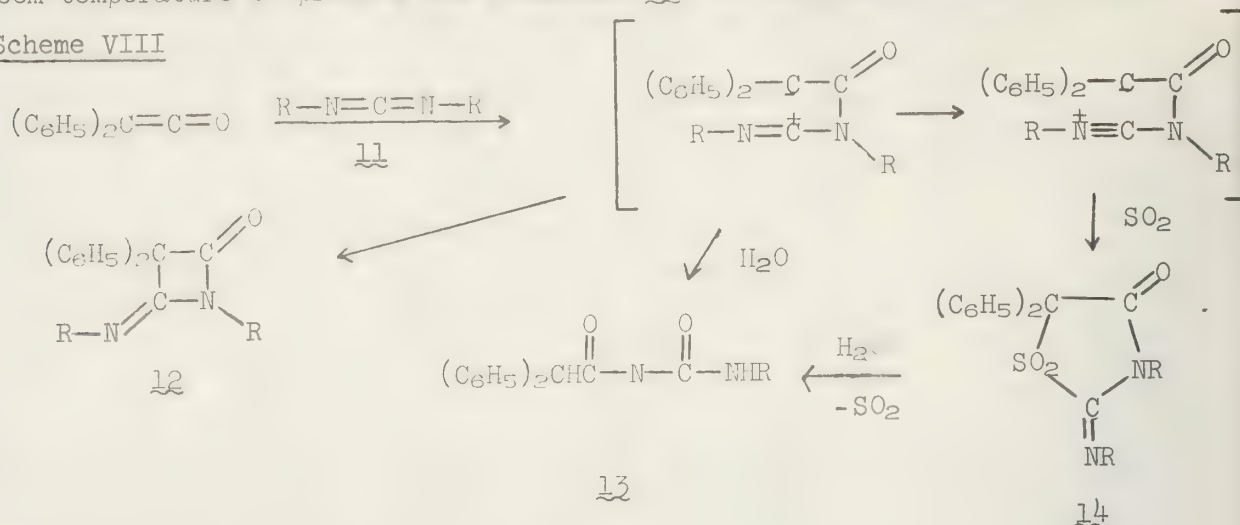
Solvent	$k \times 10^5 \text{ l. mole}^{-1} \text{ sec.}^{-1}$
Toluene	3.42 ± 0.04
THF	2.35 ± 0.05
n-Butyronitrile	1.56 ± 0.15
DMF	0.94 ± 0.05

to be 9.1 ± 0.1 kcal/mole and the entropy of activation (ΔS^*) -43.5 eu was calculated using the average rate constant $2.35 \times 10^5 \text{ l./mole sec.}$ at 40 and ΔH^* of 9.1 kcal/mole. The reaction was also run using cumene as a solvent. No dicumyl was produced but the cycloadduct was isolated in 93%. The large negative activation entropy reflects a high degree of orientation in the transition state. Solvent effect on the second order rate constant is small. The rate increases with decreasing polarity of the solvent. This would seem to indicate a highly ordered transition state with little charge separation. If a diradical intermediate were formed, a good hydrogen donor as cumene, might be expected to yield coupled product, unless the radical were short lived. Absence of dicumyl does not eliminate a diradical mechanism but suggests some other process.

The formation of cyclobutanones, bearing substituents which are in the same configuration as the original olefin, supports the concerted mechanism. Reaction of dichloroketene with cis- and trans-cyclooctenes give cis- and trans-cycloadducts respectively. The same adducts are formed when pentane or acetonitrile are used as solvents.³¹ Diphenylketene and dimethylketene have shown the same retention of configuration.^{32,33} Woodward and Hoffman have explained the evidence for the concerted mechanism of [2+2] cycloadditions from the view point of orbital symmetry conservation.²⁹

Diphenylketene undergoes [2+2] cycloaddition across the C=N double bond of imines and carbodiimides through a two step process involving a dipolar intermediate.¹⁶ Diphenylketene reacts smoothly with diisopropylcarbodiimide (11) at room temperature to produce the β -lactam (12) in 90% yield (Scheme VIII).

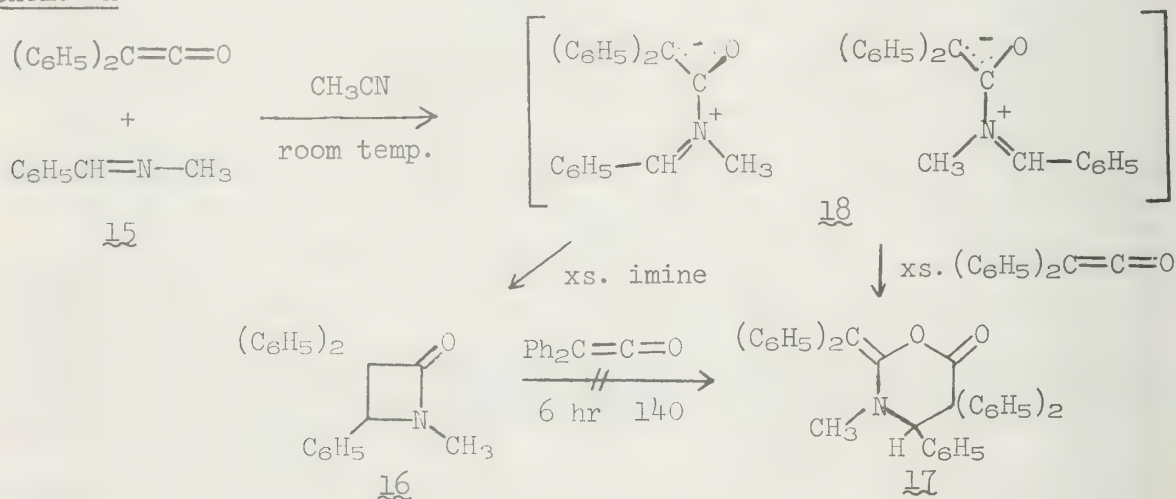
Scheme VIII



Quenching the reaction after 4 min. gave 12% of the N -phenylacetyl- N,N' -diisopropylurea (13) and (12). It was shown that under the reaction conditions, (13) was not formed from diphenylacetic acid and diisopropylcarbodiimide nor could it be produced from (12). Using liquid sulfur dioxide a quantitative yield of the thiazolidone (14) was obtained. The thiazolidone could not be produced from (12) under the reaction conditions. These facts indicate the reaction proceeds via a dipolar intermediate and the isolation of a large amount (12%) of (13) and near quantitative yield of (14) suggests the intermediate is relatively long lived.

The reaction of diphenylketene with benzylidenmethylamine (15) gives both a 1:1 adduct (16) and a 2:1 adduct (17) (Scheme IX). The β -lactam is formed in 81% yield when excess imine is used. Using excess diphenylketene, the reaction affords 82% of the oxazinone (17). When benzene is used as the solvent 71% of (16) and 95% of (17) is formed. The β -lactam does not form the 2:1 cycloadduct (17) with excess diphenylketene after 6 hours at 140. The reaction involves an open chain, dipolar intermediate (18).

Scheme IX



Since evidence for both a concerted and stepwise process for the [2+2] cycloaddition of ketenes is known, a single mechanism for all ketene cycloadditions is unlikely. The process is dependent upon the substrates involved.

CONCLUSION

Ketenes have shown wide versatility as synthetic intermediates. They have provided a general method for the preparation of cyclobutane rings, β -lactams and β -lactones. The synthetic possibilities offered by ketenes and the corresponding cycloadducts in natural product synthesis are being investigated. With the development of ketene analogues and new methods of synthesis, the now growing field of ketene chemistry is expanding faster.

BIBLIOGRAPHY

1. F. I. Luknitskii and B. A. Vovsi, Russian Chemical Reviews, 38, 487 (1969).
2. W. T. Brady, Synthesis, 415 (1971).
3. L. Ghosez, R. Montaigne, A. Roussel, H. VanLierde and P. Mollet, Tetrahedron, 27, 615 (1971).
4. W. E. Hanford and J. C. Sauer, in "Organic Reactions", 3, pp. 110 (1951).
5. N. Wilsmore, J. Chem. Soc., 1938 (1907).
6. H. Staudinger, "Die Keten", Stuttgart, 1912.
7. G. Opitz, Angew. Chem., 79, 161 (1967).
8. a. N. Sonntag, Chem. Rev., 52, 237 (1953).
b. G. Pracejus, Annalen, 622, 10 (1959).
9. a. H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain and E. J. Gaughan, J. Amer. Chem. Soc., 87, 5257 (1965).
b. L. Ghosez, R. Montaigne, P. Mollet, Tetrahedron Lett., 135 (1966).
c. W. T. Brady, H. G. Liddell and W. L. Vaughn, J. Org. Chem., 31, 626 (1966).
10. P. W. Jeffs and G. Molina, J.C.S. Chem. Comm., 3 (1973).
11. R. Montaigne and L. Ghosez, Angew. Chem. Internat. Edit. 7, 221 (1968).
12. R. E. Harmon, M. D. Barta, S. K. Gupta and G. Slomp, Chem. Comm., 89 (1970).
13. W. T. Brady and E. F. Hoff, J. Org. Chem., 35, 3733 (1970).
14. W. T. Brady and O. Waters, J. Org. Chem., 32, 3703 (1967).
15. F. Duran and L. Ghosez, Tetrahedron Lett., 245 (1970).
16. a. A. Gomes and M. M. Joullie, Chem. Comm., 935 (1970).
b. H. B. Kagan and J. L. Luche, Tetrahedron Lett., 3093 (1968).
c. R. Huisgen, B. A. Davis and M. Morikawa, Angew. Chem., 80, 802 (1968); Angew. Chem. Internat. Edit., 7, 826 (1968).
d. W. T. Brady and E. D. Dorsey, J. Org. Chem., 35, 2732 (1970).
17. H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain and E. J. Gaughan, J. Amer. Chem. Soc., 87, 5257 (1965).
18. P. D. Bartlett and T. Ando, J. Amer. Chem. Soc., 92, 7518 (1970).
19. W. T. Brady and J. P. Hieble, J. Amer. Chem. Soc., 94, 4278 (1972).
20. W. T. Brady and J. P. Hieble, Tetrahedron Lett., 3205 (1970).
21. W. T. Brady and A. D. Patel, Synthesis, 565 (1972).
22. M. C. Hoff, K. W. Greenlee and C. E. Boord, J. Amer. Chem. Soc., 73, 3329 (1951).
23. W. E. Bachman and W. S. Streive, "Organic Reactions", 1, 38 (1942).
24. M. P. Cava and B. R. Vogt, J. Org. Chem., 30, 3775 (1965).
25. P. E. Eaton and Kayson Jyi, J. Amer. Chem. Soc., 93, 2786 (1971).
26. D. Becker, Zvi Harel and Dor Birnbaum, J.C.S. Chem. Rev., 377 (1975).
27. D. Becker, M. Nagler and D. Birnbaum, J. Amer. Chem. Soc., 94, 4772 (1972).
28. Jacqueline Marchand-Brynaert and Leon Ghosez, J. Amer. Chem. Soc., 94, 2870 (1972).
29. R. B. Woodward and R. Hoffmann, "Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1969.
30. W. T. Brady and Hubert R. O'Neal, J. Org. Chem., 32, 612 (1967).
31. R. Montaigne and L. Ghosez, Angew. Chem. Internat. Edit., 7, 221 (1968).
32. R. Huisgen and G. Binsch, Angew. Chem. Internat. Edit., 3, 753 (1968).
33. J. C. Martin, V. Wilson Goodlett and Robert D. Burpitt, J. Org. Chem., 30, 4309 (1965).

ORGANIC SEMINAR ABSTRACTS

1976

SEMESTER II

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RECENT ADVANCES IN THE TOTAL SYNTHESIS
OF TETRACYCLIC AND PENTACYCLIC TRITERPENES

Reported by Mark W. Johnson

January 22, 1976

The triterpenes comprise a large and rather complex terpenoid class consisting of both pentacyclic and tetracyclic systems (Fig. 1). Synthetic work published prior to 1970 involved the coupling of identical or similar fragments in syntheses of "symmetrical" tetracyclic triterpenes.¹ Progress toward the synthesis of "unsymmetrical" triterpenes has been inhibited to a great extent by the inherent problems of stereochemical control in the elaboration of these molecules. For example, the common pentacyclic triterpenes contain up to eight tertiary or quaternary asymmetric centers at ring junctions.¹

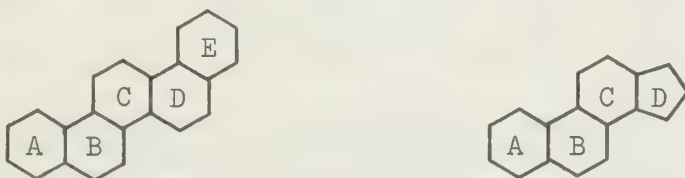


Fig. 1

Recent approaches to the synthesis of tetra- and pentacyclic triterpenes can be classified into two basic categories: 1) a classical synthetic approach involving modifications of functional groups of readily available compounds to obtain the target molecules, and 2) a non-enzymic, biogenetic-like polyene cyclization approach, as exemplified by the work of Johnson and van Tamelen.^{1,2}

Examples of the classical approach were Stork's 1971 synthesis of lupeol, a pentacyclic triterpene,³ in which a key intermediate was a tricyclic compound which provided the CDE rings of lupeol, and Johnson and Ireland's 1970 synthesis of germanicol,⁴ another pentacyclic compound, in which a tricyclic intermediate provided the A, B, and C rings.

The intermediates that Ireland used in his 1973 synthesis of alnusenone⁵ and, with slight modifications, in his more recent synthesis of shionone^{6,7,8} contained an aromatic A ring which was used in an intramolecular Friedel-Crafts cycloalkylation. A mechanistic study of the stereochemical outcome of this key reaction appeared earlier.⁹ Several other formal total syntheses using the classical approach have also been reported,¹⁰⁻¹⁴ as well as syntheses of several other compounds which are potential intermediates for a number of pentacyclic and a few tetracyclic triterpenes.¹⁵⁻²¹

Examples of the biogenetic-like approach can be found in the work of Prestwich and Labovitz, who have recently succeeded in synthesizing serratenediol via a series of biogenetic-like cyclizations,²² and that of Ireland, who has recently reported an alternative total synthesis of alnusenone via polyene cyclization²³ as well as a study on the use of the polyene cyclization approach to generate tetradecahydronicene derivatives for pentacyclic triterpene synthesis.²⁴

BIBLIOGRAPHY

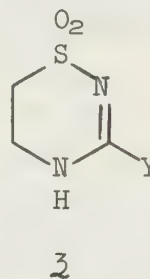
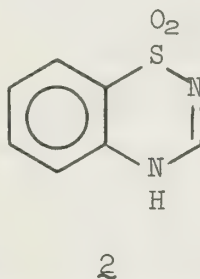
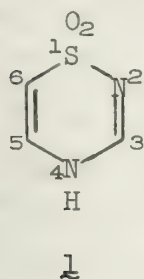
1. For a review of early synthetic work see: J. W. ApSimon and J. W. Hooper, "The Synthesis of Triterpenes", in The Total Synthesis of Natural Products, Vol. II, J. W. ApSimon, ed., Wiley-Interscience, New York, 1973, p. 559.
2. E. E. vanTamelen, Acc. Chem. Res., 8, 152 (1975).
3. G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, J. Labovitz, J. Am. Chem. Soc., 93, 4945 (1971).
4. R. E. Ireland, S. Baldwin, D. Dawson, M. Dawson, J. Dolfini, J. Newbould, W. S. Johnson, M. Brown, R. Crawford, P. Hurdlik, G. Rasmussen, and K. Schmiegel, ibid., 92, 5743 (1970).
5. R. E. Ireland, M. Dawson, S. Welch, A. Hagenbach, J. Bordner, and B. Trus, ibid., 95, 7829 (1973).
6. R. E. Ireland, C. Lipinski, C. Kowalski, J. Tilley, and D. Walba, ibid., 96, 3333 (1974).
7. R. E. Ireland, M. Dawson, C. Kowalski, C. Lipinski, D. Marshall, J. Tilley, J. Bordner, and B. Trus, J. Org. Chem., 40, 973 (1975).
8. R. E. Ireland, C. Kowalski, J. Tilley, and D. Walba, ibid., 40, 990 (1975).
9. R. E. Ireland, S. Baldwin, and S. Welch, J. Am. Chem. Soc., 94, 2056 (1972).
10. K. Waisser, J. Urban, and A. Vystrčil, Collect. Czech. Chem. Commun., 40, 452 (1975).
11. K. Tachibana and T. Takahashi, Tetrahedron Lett., 1857 (1975).
12. K. Iguchi and H. Kakisawa, Chem. Commun., 1486 (1970).
13. G. Stork, A. Meisels, and J. E. Davies, J. Am. Chem. Soc., 85, 3419 (1963).
14. D. H. R. Barton, E. F. Lier, and J. F. McGhie, J. Chem. Soc. (C), 1031 (1968).
15. C. H. Heathcock and J. E. Ellis, Chem. Commun., 1474 (1971).
16. J. S. Dutcher, J. G. MacMillan, and C. H. Heathcock, Tetrahedron Lett., 929 (1974); J. S. Dutcher and C. H. Heathcock, ibid., 933 (1974).
17. C. H. Heathcock, Syn. Commun., 4, 71 (1974).
18. J. W. ApSimon, P. Baker, J. Buccini, J. W. Hooper, and S. Macaulay, Can. J. Chem., 50, 1944 (1972).
19. W. G. Dauben, G. Ahlgren, T. J. Leitereg, W. C. Schwarzel, and M. Yoshioko, J. Am. Chem. Soc., 94, 8593 (1972).
20. R. E. Ireland and U. Hengartner, ibid., 94, 3652 (1972).
21. J. T. Pinhey, J. J. H. Simes, et al., J. Chem. Soc. Perkin Trans. I, 2260 (1972).
22. G. D. Prestwich and J. N. Labovitz, J. Am. Chem. Soc., 96, 7103 (1974).
23. R. E. Ireland, P. Bey, K. Cheng, R. J. Czarny, J. Moser, and R. I. Trust, J. Org. Chem., 40, 1000 (1975).
24. R. E. Ireland, T. C. McKenzie, and R. I. Trust, ibid., 40, 1007 (1975).

THE THIADIAZINE RING SYSTEM: 1,2,4-(4H)-THIADIAZINE 1,1-DIOXIDES

Reported by David House

February 2, 1976

The 1,2,4-thiadiazine 1,1-dioxide ring system, **1**, is a six-membered heterocyclic ring containing two nitrogen atoms and one sulfur atom. This ring system has been known since 1902, when the fused 1,2,4-benzothiadiazine 1,1-dioxides, **2**, were first reported as a class of compounds,¹ and considerable effort has been expended on the fused-ring system, which has been found to be very useful medically.²⁻⁶

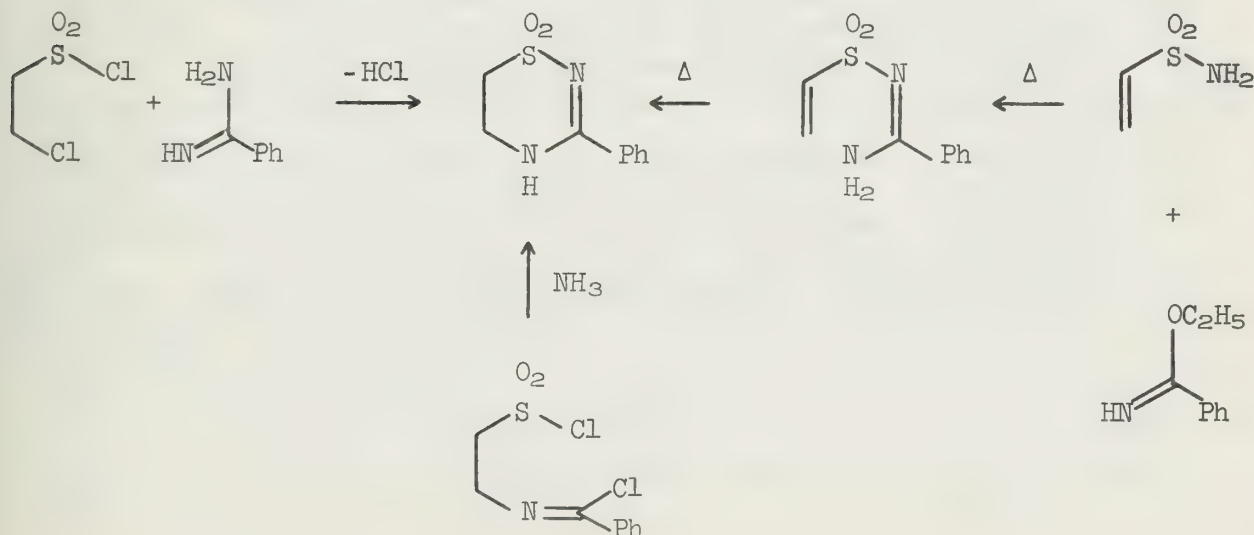


The present seminar will review the simpler class, the 1,2,4-thiadiazine 1,1-dioxides themselves. Much of the work in this area has been carried out in the last ten years, with one of the earliest preparations reported in 1947.⁷ Though there have been no reviews on the non-fused ring system, the system was mentioned briefly in a review in 1970.⁸

By varying the starting materials the degree of unsaturation in the ring can be easily controlled as well as the locations of any double bonds exocyclic to the ring.⁹ Several useful syntheses of the 1,2,4-thiadiazine 1,1-dioxides have been reported, and almost all of them have reported moderate to good yields.^{7,10-14} Representative examples are shown in Scheme 1.

As one might suspect, the 1,2,4-(4H)-thiadiazine 1,1-dioxides are capable of tautomerization with the 2H form, and this has often been a point of confusion in the literature; however, studies have shown that where tautomerization is possible, the 4H form is almost always the predominant tautomer.^{10-12,15,16}

Scheme 1



1,2,4-Thiadiazine 1,1-dioxides substituted at the 4-position may be synthesized directly from the unsubstituted (4H)-thiadiazine 1,1-dioxides or may be made directly by judicious choices of starting materials.^{13,17-19} In addition, reaction may occur at either the 2- or the 4-position, depending upon the reaction conditions.^{18,19} The reactions of the 1,2,4-(4H)-thiadiazine 1,1-dioxides can be illustrated by the studies of LeBerre and coworkers,²⁰ in which 3 ($\text{Y} = -\text{SR}$ or $-\text{OR}$) is a typical starting material.

Like the fused-ring benzothiadiazine 1,1-dioxides, the simple 1,2,4-(4H)-thiadiazine 1,1-dioxides have been found potentially useful in medicine, for example, as analgesic and anti-hypertensive agents,²¹ as diuretics,¹⁰ and as phytosanitary agents in agriculture.¹⁴

BIBLIOGRAPHY

1. B. Ekbom, *Svensk Vetenskakad Handl.*, 27, 3 (1902); F. C. Norvello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, 25, 970 (1960).
2. C. T. Holdrege, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.*, 81, 4807 (1959).
3. J. G. Topliss, M. H. Sherlock, F. H. Clarke, M. C. Daly, B. W. Pettersen, J. Lipski, and N. Sperber, *J. Org. Chem.*, 26, 3842 (1961).
4. M. DiBella, M. Rinaldi, V. Fabio, and G. Manicardi, *Farmaco, Ed. Sci.*, 28, 411 (1973); *Chem. Abstr.*, 79, 32018j (1974).
5. A. Castro and D. P. Grettie, *Biochem. Med.*, 9, 354 (1974).
6. M. Moser, *Amer. Heart J.*, 791 (1974); *Chem. Abstr.*, 81, 114273u (1974).
7. R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, 69, 1393 (1947); footnote 18.
8. A. Lawson and R. B. Tinkler, *Chem. Rev.*, 70, 593 (1970).
9. G. Vampa, M. Melegari, and A. Albasini, *Atti Soc. Natur. Mat. Modena.*, 102, 83 (1971); *Chem. Abstr.*, 80, 120878r (1974).
10. W. L. Matier, W. T. Comer, and A. W. Gomoll, *J. Med. Chem.*, 17, 549 (1974).
11. W. L. Matier and W. T. Comer, *J. Org. Chem.*, 39, 3080 (1974).
12. K. Hasegawa and S. Hirooka, *Bull. Chem. Soc. Jpn.*, 45, 1893 (1972).
13. A. Étienne, A. Le Berre, and J. -P. Giorgetti, *Bull. Soc. Chim. Fr.*, 985 (1973).
14. A. Le Berre, A. Étienne, and J. Prades, *Fr.* 2,036,528 (1970); *Chem. Abstr.*, 75, 88652w (1971).
15. R. C. Elderfield, Ed., "Heterocyclic Compounds," Volume 7, John Wiley and Sons, Inc., New York, N. Y., 1961, p 823.
16. F. C. Norvello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, 25, 970 (1960).
17. L. Toldy and P. Sohár, *Tetrahedron Lett.*, 181 (1970).
18. A. Étienne, A. Le Berre, and J. -P. Giorgetti, *Bull. Soc. Chim. Fr.*, 1395 (1974).
19. A. Étienne, A. Le Berre, and J. -P. Giorgetti, *Bull. Soc. Chim. Fr.*, 1917 (1974).
20. A. Étienne, A. Le Berre, and J. -P. Giorgetti, *Bull. Soc. Chim. Fr.*, 2361 (1973).
21. W. L. Matier and W. T. Comer, *Ger.* 2,428,222 (1975); *Chem. Abstr.*, 82, 170959e (1975).

BORANE-TETRAHYDROFURAN AND BORANE-METHYL SULFIDE:
EXCEPTIONALLY MILD AND SELECTIVE REDUCING AGENTS FOR CARBOXYLIC ACIDS

Reported by John M. Zeigler

February 5, 1976

The chemist is often faced with the problem of reducing a single functional group in the presence of other reducible functions. Recently, it has been recognized that borane--complexed with tetrahydrofuran or methyl sulfide--is a mild, selective reducing agent for a variety of functions. These complexes, which had already proved their utility as hydroborating agents,¹⁻⁵ were found to reduce a wide range of groups under mild conditions.^{3,4,6} The relative reactivity of borane-tetrahydrofuran with common functions was found to decrease in the following order: carboxylic acids \geq olefins $>$ ketones $>$ nitriles $>$ epoxides $>$ esters $>$ acid chlorides.^{3,6} A similar order has been observed for borane-methyl sulfide.^{4,5,7,23} The rapid reduction of carboxylic acids has been rationalized in terms of a resonance contributor in the intermediate triacyloxyborane which serves to activate the carbonyl toward reduction.^{3,6,8}

Borane is unusual as a reducing agent in that it is electrophilic in nature. Thus, electron-rich acids are reduced more rapidly than electron-poor acids. The synthetic advantages which accrue from the electrophilic character of borane have been pointed out on numerous occasions.^{1,3,6,7,8}

The observation of rapid, nearly quantitative reduction of carboxylic acids to the corresponding alcohols by borane under mild conditions quickly led to studies of the possibilities for the selective reduction of the carboxyl function. Brown, *et al.*,⁸ have studied the reduction of difunctional carboxylic acids with borane-tetrahydrofuran. Their results are compared, where possible, with those of Lane, *et al.*,^{7,13a} using borane-methyl sulfide as reducing agent in Table 1. The yields and relative rates of

Table 1. Reduction of Difunctional Carboxylic Acids
with Borane Complexes^{7,8,13a}

Acid	Product Alcohol	BH ₃ -THF		BH ₃ -Me ₂ S	
		Yield ^a	Conditions ^b	Yield ^a	Conditions ^{b,c}
2-iodobenzoic	2-iodobenzyl	92	0°, 1 hr	100	r.t., 4 hr
2-bromobenzoic	2-bromobenzyl	93		88	
benzoic	benzyl	89		54	
salicylic	2-hydroxybenzyl	92		99	r.t., 17 hr
1-adamantyl	1-adamantane-methanol	95		--	-----
11-bromo-undecanoic	11-bromo-undecanol	91		94	r.t., 2.5 hr
4-nitrophenyl-acetic	2-(4-nitrophenyl)-ethanol	94		--	-----
adipic	1,6-hexanediol	100	0°, 6 hr	--	-----
ethyl hydrogen adipate	ethyl 6-hydroxy-hexanoate	88	-18°, 16 hr	--	-----
4-aminobenzoic	4-aminobenzyl	80	0°, 4.5 hr	--	-----

^a% isolated ^bTHF used as solvent
trimethyl borate

^cPerformed in the presence of excess

reduction have been shown to be insensitive to a change of aprotic solvent.^{7,8} As can be seen, the yields are comparable, although borane-methyl sulfide reductions are slower and must be run at room temperature or slightly higher. Borane-methyl sulfide has several practical advantages over borane-tetrahydrofuran: as commercially supplied,¹² it has a molar concentration ten times that of borane-tetrahydrofuran; is stable indefinitely when refrigerated; and is less than half as expensive per mole of borane.^{13a,b} Both complexes can be handled safely in air.

Borane, mainly as the tetrahydrofuran complex, has been successfully applied to a number of interesting specific reductions. It has been used to reduce carboxyl groups in the presence of esters,^{8,10,14,15} quinones,¹⁶ and sulfoxides.¹⁷ The most interesting applications have been with biochemically important compounds, where the mildness and selectivity of the reagent have made it a natural choice. It has proved possible to reduce selectively carboxyl groups in amino acids,²⁴ proteins and polypeptides,^{9,19,20} carbohydrates,²¹ and in the synthesis of vitamin B₆ (pyridoxine)²² and a chloramphenicol derivative.²⁵ From these examples, it seems apparent that borane is a very powerful synthetic tool whose potential is only beginning to be explored.

BIBLIOGRAPHY

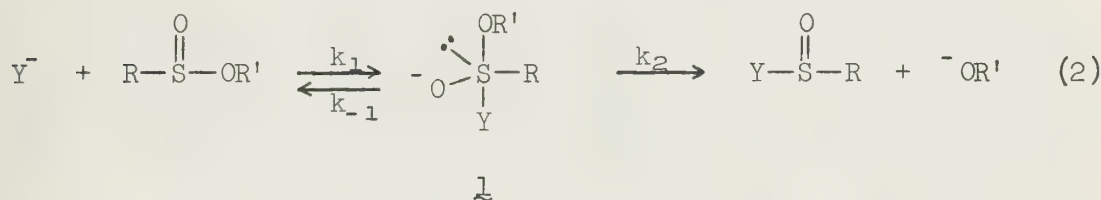
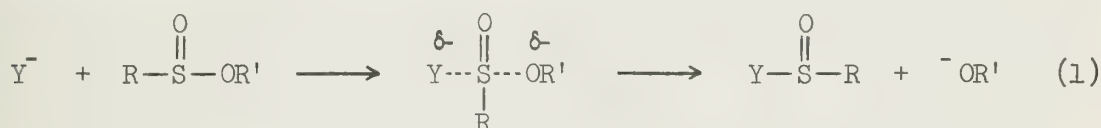
1. H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, 1972, p 227f.
2. H. C. Brown and B. C. Subba Rao, J. Am. Chem. Soc., 81, 6428 (1959).
3. H. C. Brown and B. C. Subba Rao, J. Am. Chem. Soc., 82, 681 (1960).
4. L. M. Braun, R. A. Braun, H. R. Crissman, M. Opperman, and R. M. Adams, J. Org. Chem., 36, 2388 (1971).
5. C. F. Lane, J. Org. Chem., 39, 1437 (1974).
6. H. C. Brown, P. Heim, and N. M. Yoon, J. Am. Chem. Soc., 92, 1637 (1970).
7. C. F. Lane, H. L. Myatt, J. Daniels, and H. B. Hopps, J. Org. Chem., 39, 3052 (1974).
8. H. C. Brown, S. Krishnamurthy, T. P. Stocky, N. M. Yoon, and C. S. Pak, J. Org. Chem., 38, 2786 (1973).
9. M. Z. Atassi and A. F. Rosenthal, Biochem. J., 111, 593 (1969).
10. S. Hagashita and K. Kuriyama, Tetrahedron, 28, 1435 (1972).
11. A. Pelter, M. G. Hutchings, T. E. Levitt, and K. Smith, Chem. Commun., 347 (1970).
12. Aldrich Chemical Company.
13. (a) C. F. Lane, Aldrichimica Acta, 8, 20 (1975); (b) D. R. Harvey, *ibid.*, 8, 39 (1975).
14. M. Fetizon and N. Moreau, Bull. Soc. Chim. Fr., 4385 (1969).
15. N. L. Allinger and L. A. Tushaus, J. Org. Chem., 30, 1945 (1965).
16. D. S. Bapat, B. C. Subba Rao, M. K. Unni, and K. Venkataraman, Tetrahedron Lett., 15 (1960).
17. S. Ghersetti, H. Hogaveen, G. Maccagani, F. Montenari, and F. Taddei, J. Chem. Soc., 3718 (1963).
18. D. G. M. Diaper and W. M. J. Strachan, Can. J. Chem., 45, 33 (1967).
19. M. Z. Atassi and M. F. Perlstein, Biochem., 11, 3984 (1972).
20. M. Z. Atassi and E. J. Nakhleh, Biochim. Biophys. Acta, 379, 1 (1975).
21. S. C. McKee and E. E. Dickey, J. Org. Chem., 28, 1561 (1963).
22. R. A. Firestone, E. E. Harris, and W. Reuter, Tetrahedron, 23, 943 (1967).
23. C. F. Lane and H. Myatt, unpublished results.
24. M. L. Anhoury, M. Arickx, P. Crooy, R. De Neys, and J. Eliaers, J. Chem. Soc., Perkin I, 191 (1974).
25. C. K. Wat, V. S. Malik, and L. C. Vining, Can. J. Chem., 49, 3653 (1971).

NUCLEOPHILIC ATTACK ON SULFUR IN SULFONATES, SULFINATES, AND SULFENATES

Reported by Charles S. Donley

February 9, 1976

It has long been known that esters of sulfinic and sulfonic acids can undergo carbon-oxygen or sulfur-oxygen bond cleavage from solvent or added nucleophiles. Until recently, sulfenic esters were thought to undergo only sulfur-oxygen bond cleavage. Nucleophilic substitution at sulfur in these systems is particularly interesting because of the question of timing of bond breaking and bond formation in the rate determining step. Two conceivable mechanisms are possible (exemplified by a sulfinates), one involving concerted bond making and breaking analogous to an S_N2 substitution at carbon (eq 1) and the other involving a hypervalent sulfur trigonal-bipyramidal (TBP) intermediate, 1, (eq 2).



In general, alkyl sulfonates predominantly undergo C-O bond cleavage, usually by an S_N2 mechanism at carbon, to give alkyl derivatives of the attacking nucleophile, as seen recently, for example, in the reaction of hydrogen peroxide with n-butyl methanesulfonate.¹ Exceptions are aromatic and neopentyl sulfonate esters, which can easily undergo S-O bond cleavage depending on choice of solvent and nucleophilic reagent. Use of polarizable nucleophiles such as thiophenoxide and acetoacetic ester anion results in high ratios of C-O cleavage for various nitrophenyl tosylates, whereas S-O bond cleavage occurs with methoxide.² Likewise, neopentyl tosylate undergoes S-O cleavage with methoxide but C-O cleavage with thiophenoxide.³ With dimsyl anion and phenyl tosylate in dimethyl sulfoxide S-O cleavage was observed.⁴ Use of hexamethylphosphoramide gave C-O cleavage even with neopentyl tosylate.⁵ Cyclic sulfonate esters (sultones) have been shown to undergo S-O cleavage by hydroxide^{6,7} or by methoxide⁷ in aqueous systems.

Instances of S-O bond cleavage in sulfinates are more numerous, since the sulfinates anion is not as good a leaving group as sulfonate. By the use of ¹⁸O tracer studies, it was established early that methyl p-toluenesulfinate undergoes acid- or base-catalyzed hydrolysis with S-O bond cleavage⁸ as does benzhydryl p-toluenesulfinate.⁹ The ethanolysis of 2-p-anisyl-2-methylpropyl arenesulfinates was also found to involve S-O cleavage and base catalysis.¹⁰ Other studies,¹¹⁻¹³ particularly those involving the formation of sulfones, clearly indicated that C-O cleavage takes place and ionization mechanisms leading to a sulfinates anion and a carbonium ion have been proposed. Recently, reaction parameters were determined for the hydrolysis of ethyl p-substituted benzenesulfinates which underwent S-O cleavage.¹⁴ Acid-catalyzed reactions, for example, were found to have $\rho = -0.54$ (at 20°), while the reactions in alkaline media were found to have $\rho = 1.60$.

Sulfenates undergo S-O bond cleavage, as is expected in view of the poor leaving group ability of the sulfenate anion. Braverman¹⁵ has recently found, however, that the ethanolysis of *p*-anisyl trichloromethanesulfenate undergoes C-O cleavage to form *p*-anisyl ethyl ether and dichlorosulfine, $\text{Cl}_2\text{C}=\text{SO}$, and has suggested that the solvolysis proceeds by an ionization mechanism to some ion-pair species. A study¹⁶ of the reactions of *p*-substituted triphenylmethanesulfenates with hydroxide and *p*-substituted phenoxides led to the conclusion that the mechanism involved an $\text{S}_{\text{N}}2$ -type substitution at sulfur. A subsequent report,¹⁷ however, indicated that with nitrogen nucleophiles the reaction proceeded via a two step addition-elimination mechanism.

The studies described above have not as yet resolved the mechanism for nucleophilic attack at sulfur. Bender¹⁸ demonstrated the existence of a tetrahedral intermediate in the hydrolysis of carboxylates by observing isotopic exchange between carbonyl ^{18}O -labeled ester and solvent after partial hydrolysis. In attempting to find evidence for a TBP intermediate (e.g., 1), similar experiments^{19,20} using ^{18}O tracers have shown no isotopic exchange with solvent. Kice,²¹ however, has pointed out in his study of the exchange of methoxy groups between methanol- d_3 and methyl *p*-toluenesulfinate that the absence of isotopic exchange does not preclude the existence of a TBP intermediate. Proton transfer between oxygens may be energetically unfavorable unless equilibration of oxygens can occur via a pseudorotation process. This process is probably much slower than the breakdown of the intermediate (k_1 and k_2 in eq 2) as was shown in the case of the intermediate in the hydrolysis of methyl ethylene phosphate.²²

BIBLIOGRAPHY

1. N. A. Radomsky and M. J. Gibian, *J. Am. Chem. Soc.*, **95**, 8713 (1973).
2. J. F. Bunnett and J. Bassett, Jr., *ibid.*, **81**, 2104 (1959).
3. F. Bordwell, B. Pitt, and M. Knell, *ibid.*, **73**, 5004 (1951).
4. T. Broxton, Y. Mac, A. J. Parker, and M. Ruane, *Aust. J. Chem.*, **19**, 521 (1966).
5. B. Stephenson, G. Solladié, and H. S. Mosher, *J. Am. Chem. Soc.*, **94**, 4184 (1972).
6. (a) E. T. Kaiser and O. R. Zaborsky, *ibid.*, **90**, 4626 (1968); (b) O. R. Zaborsky and E. T. Kaiser, *ibid.*, **92**, 860 (1970).
7. J. H. Smith, T. Inoue, and E. T. Kaiser, *ibid.*, **94**, 3098 (1972).
8. C. A. Bunton and B. N. Hendy, *J. Chem. Soc.*, 2562 (1962).
9. C. A. Bunton and B. N. Hendy, *ibid.*, 627 (1963).
10. D. Darwish and J. Noreyko, *Can. J. Chem.*, **43**, 1366 (1965).
11. A. H. Wragg, J. S. McFadyen, and T. S. Stevens, *J. Chem. Soc.*, 3603 (1958).
12. (a) D. Darwish and R. A. McLaren, *Tetrahedron Lett.*, 1231 (1962); (b) D. Darwish and E. A. Preston, *ibid.*, 113 (1964).
13. (a) S. Braverman and S. Steiner, *Isr. J. Chem.*, **5**, 267 (1967); (b) S. Braverman and T. Globberman, *Tetrahedron*, **30**, 3873 (1974).
14. M. Kobayashi, R. Nishi, and H. Minato, *Bull. Chem. Soc. Jpn.*, **47**, 888 (1974).
15. S. Braverman and D. Reisman, *Tetrahedron*, **30**, 3891 (1974).
16. L. Senatore, E. Ciuffarin, and A. Fava, *J. Am. Chem. Soc.*, **92**, 3035 (1970).
17. E. Ciuffarin, L. Senatore, and M. Isola, *J. Chem. Soc. B*, 2187 (1971).
18. M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).
19. C. A. Bunton, P. D. B. de la Mare, P. M. Greasley, D. R. Llewellyn, N. H. Pratt, and J. G. Tillett, *J. Chem. Soc.*, 4751 (1958).
20. A. A. Najam and J. G. Tillett, *J. Chem. Soc., Perkin II*, 858 (1975).
21. J. L. Kice and C. A. Walters, *J. Am. Chem. Soc.*, **94**, 590 (1972).
22. R. Kluger, F. Covitz, E. Dennis, L. D. Williams, and F. H. Westheimer, *ibid.*, **91**, 6066 (1969).

PROTON TRANSFER REACTIONS IN THE PHOTOEXCITED STATE

Reported by Terry Lewis

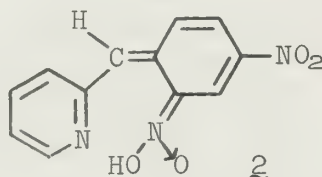
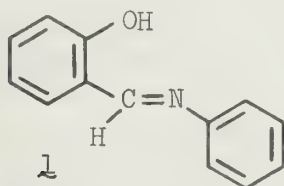
February 16, 1976

Extensive evidence shows that in many aromatic species the excited states are much stronger acids or bases than the ground states.^{1,2} This enhanced activity may be correlated with the modified charge distribution in the lowest excited singlet state ($\pi \rightarrow \pi^*$), as exemplified by the increased polarizability of the excited state species.³⁻⁶ From quantitative data obtained on excited state pK' 's of numerous aromatic acids and bases, the dramatic effects of light-induced ionization are shown. For example, in the case of β -naphthol, an increase in acidity of six orders of magnitude has been observed as a result of photoexcitation.¹

Saeva and Olin have reported⁷ recently a novel utilization of a photoexcited state to initiate a ground state reaction. Nitrosation of sodium 2-naphthol-6-sulfonate in neutral aqueous solution and subsequent diazo coupling with a variety of 4-substituted anilines have been initiated photochemically in the presence of sodium nitrite.

A major class of photochromic reactions,⁸⁻¹¹ reversible color changes induced by light, involves excited state proton transfers, usually in the form of prototropic tautomerism. These photochromic proton transfer reactions generally have several features in common:⁹ 1) an intramolecular proton transfer photolysis step occurs via a six-membered transition state; 2) the thermally stable forms are ortho-substituted aromatic structures; 3) the photochemical proton transfer produces a quinoid-type structure; 4) one of the initial ortho substituents is a polar group whose excited state has greatly enhanced reactivity compared with the other group; and 5) one or more processes occur to cause some stabilization of the photo-colored species formed by the endothermic photolysis step. In several cases, the photochromic behavior of a compound in solution differs markedly from that of the compound in the solid state. The reactivity peculiar to the solid state has been analyzed in terms of topochemical control available in the crystal lattice.¹²

A large number of salicylaldehyde anils (general structure 1) have been reported to be photochromic both in solution and in the solid state.¹³ Although the exact photochromic mechanism remains a controversy,¹⁴⁻¹⁶ it is generally agreed that the first step involves excited state proton transfer to form a cis-quinoid-type structure, followed by rotation around one or more bonds to give the colored species observed. The extent of the bond rotation as well as the exact nature of the colored product remain unresolved. Of those anils photoactive in solution, only a particular crystalline modification, in which the packing arrangement allows for reorientation, exhibits photoactivity in the solid state.^{17,18} Other anils (general formula $\text{Ar}-\text{CH}=\text{N}-\text{Ar}$) have also been studied.¹⁹



Both 2- and 4-(2',4'-dinitrobenzyl)-pyridines, α - and γ -DNBP, respectively, are photochromic in solution, but only α -DNBP is photoactive in the solid state.²⁰ The mechanism seems to involve initial proton transfer to the o-nitro group, producing an aci-nitro quinoid, such as 2, which subsequently can undergo acid-base equilibration with the pyridine nitrogen.²⁰ The

second step of this process is prohibited within the crystal lattice of γ -DNBP,²¹ apparently accounting for the lack of photosensitivity. X-Ray data suggest that the second proton transfer is feasible in the solid state for α -DNBP.²²

Other recently reported photochromic systems involving excited state proton transfers as a primary process include 2-hydroxy- α, α -diphenyl-benzenemethanol,²³ salicylaldehyde 2-quinolylylhydrazone,²⁴ and the hydrate of 2-(1-hydroxy-4,5-dimethyl-1H-imidazol-2-yl)-6-methylpyridine.²⁵

REFERENCES AND NOTES

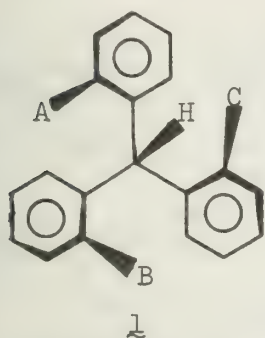
1. A. Weller, Z. Phys. Chem. (Frankfurt am Main), 3, 238 (1955).
2. G. Jackson and G. Porter, Proc. R. Soc. London, Ser. A, 260, 13 (1961).
3. G. Porter, in "Reactivity of the Photoexcited Organic Molecule," Proceedings of the Thirteenth Conference on Chemistry at the University of Brussels, October, 1965, Interscience Publishers, New York, N. Y., 1967, pp 93-101.
4. J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, pp 550-555.
5. C. A. Parker, "Photoluminescence of Solutions," Elsevier, Amsterdam, 1968, pp 328-344.
6. For examples of the effect of photoexcited state charge distribution on photosubstitution reactions of aromatic compounds, see J. Cornelisse and E. Havinga, Chem. Rev., 75, 353 (1975).
7. F. D. Saeva and G. R. Olin, J. Am. Chem. Soc., 97, 5631 (1975).
8. R. Exelby and R. Grinter, Chem. Rev., 65, 247 (1965).
9. J. D. Margerum and L. J. Miller, in "Techniques of Chemistry," G. H. Brown, Ed., Vol. 3, Wiley-Interscience, New York, N. Y., 1971, pp 558-591.
10. D. R. Arnold, et al., "Photochemistry, An Introduction" Academic Press, Inc., New York, N. Y., 1974, pp 238-262.
11. For potential uses of photochromic systems in non-conventional imaging processes, see M. R. V. Sahyun, J. Chem. Educ., 50, 88 (1973); D. S. Lo, Appl. Opt., 13, 861 (1974).
12. For examples of topochemical control in solid state photochemical dimerizations, see M. Baillargeon, Univ. of Il. Org. Sem. Abst., 36 (Fall 1975).
13. M. D. Cohen, G. M. J. Schmidt, and S. Flavian, J. Chem. Soc., 2041 (1964).
14. R. Potashnik and M. Ottolenghi, J. Chem. Phys., 51, 3671 (1969).
15. R. S. Becker and W. F. Richey, J. Am. Chem. Soc., 89, 1298 (1967).
16. T. Rosenfeld, M. Ottolenghi, and A. Y. Meyer, Mol. Photochem., 5, 39 (1973).
17. J. Bregman, L. Leiserowitz, and G. M. J. Schmidt, J. Chem. Soc., 2068 (1964).
18. J. Bregman, L. Leiserowitz, and K. Osaki, J. Chem. Soc., 2086 (1964).
19. E. Hadjoudis and E. Hayon, J. Phys. Chem., 74, 3184 (1970); E. Hadjoudis, Mol. Cryst. Liq. Cryst., 13, 233 (1971).
20. D. Ben-Hur and R. Hardwick, J. Chem., Phys., 57, 2240 (1972), and references cited therein.
21. T. Ottersen and K. Seff, Acta Crystallogr., Sect. B, 30, 955 (1974).
22. K. Seff and K. N. Trueblood, Acta Crystallogr., Sect. B, 24, 1406 (1968).
23. S. Hamai and H. Kokubun, Z. Phys. Chem. (Frankfurt am Main), 88, 211 (1974); Bull. Chem. Soc. Jpn., 47, 2085 (1974); *ibid.*, 48, 798 (1975).
24. J. L. Wong and F. N. Bruscatto, Tetrahedron Lett., 4593 (1968); J. L. Wong and M. F. Zady, J. Chem. Soc. Chem. Commun., 684 (1973); J. L. Wong and M. F. Zady, J. Org. Chem., 40, 2512 (1975).
25. G. G. Allan, et al., J. Phys. Chem., 77, 2160 (1973).

HINDERED ROTATION IN TRIARYLMETHANES

Reported by Barbara J. Mann

February 19, 1976

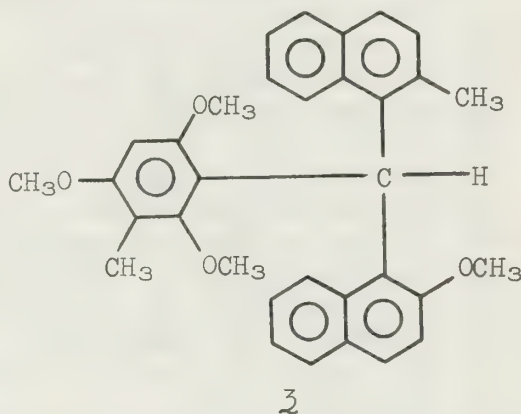
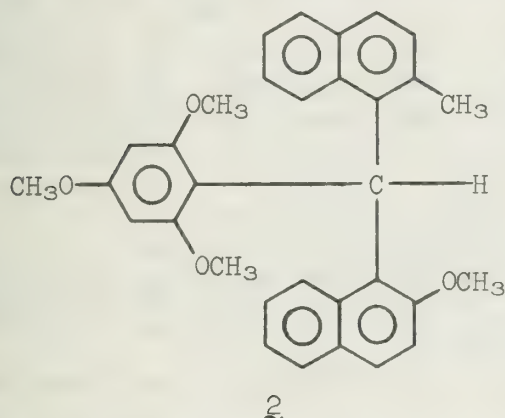
Triarylmethanes and similar compounds present an excellent opportunity to study isomerism and isomerization in sterically congested molecules. Bulky substituents on the aryl rings can result in hindered rotation about the aryl-methine bond.¹⁻³ In all triarylmethanes and cognates studied thus far, the molecule in the ground state assumes a propeller conformation in which the aryl rings have the same sense of twist.⁴ Figure 1 depicts one of several possible propeller forms. X-Ray studies of the crystalline state,^{1,5-9} electron diffraction studies of the gaseous phase,¹⁰ and ¹H nuclear magnetic resonance solution studies^{2,5,11-15} of triarylmethanes are all consistent with a propeller conformation.



Analysis of the static stereochemistry of triarylmethanes reveals a complex situation if $A \neq B \neq C$.¹⁶ Since the central atom is chiral a racemic pair exists. Also, there is a plane of chirality defined by the three carbon atoms of the aryl rings which are attached to the central atom. All three substituents A, B, and C may be on the same side of this plane or one may be on the opposite side from the other two in a relationship much like cis-trans isomerism. Independent of these, there is an axis of chirality, through the central carbon atom and perpendicular to the plane of chirality, which defines the sense of twist of the propeller. The possibility of

32 isomers (16 racemic pairs) thus exists in this system. Degeneracies occur whenever two or more of the aryl rings are identical or when a ring is symmetrically substituted with respect to the plane of chirality.

The temperature-dependent ¹H nmr spectra of triarylmethanes indicate that a variety of interconversions of stereoisomeric molecules is occurring.^{17,18} One of the more complicated systems to be investigated, 2,¹⁹ shows a multitude



of methoxyl signals at low temperatures, indicating that a mixture of many isomers is present on the nmr time scale. As the temperature increases many of the signals coalesce until at 37° only four methoxyl signals, in the ratio 1:1:1:1, remain. Raising the temperature to 191° causes no further coalescence. Even at high temperatures, when rotation of all aryl rings is expected to be fast, the two o-methoxy groups remain diastereotopic. This is an example of residual diastereotopicity, which arises because the aryl rings do not rotate independently but in a correlated fashion with two rings rotating in one direction and the third ring rotating in the opposite direction. This correlated rotation results in two distinct sets of averaged o-methoxy environments for 2.

Compound **3** exists in two diastereomeric forms even when rotation of all the aryl rings is fast.²⁰ The two diastereomers have been separated by fractional recrystallization. Each of the diastereomers consists of a rapidly interconverting equilibrium mixture of eight propeller structures. This is an example of residual stereoisomerism which, like residual diastereotopicity, exists because of the correlated fashion in which the aryl rings rotate.²¹

In addition to triarylmethanes, a large number of other chemical systems display this type of stereoisomerism such as Ar_3Z ($\text{Z} = \text{C}^+, \text{C}^*, {}^{12,22-25} \text{N}, {}^{26} \text{B}, {}^5 \text{As}, \text{SiH}^{27-29}$), Ar_2ZX_2 ($\text{ZX}_2 = \text{CH}_2, \text{C=O}$), and certain transition metal tris chelates.³⁰ All of these may be classed as molecular propellers and their static and dynamic stereochemistry can be analyzed in the same way.³⁰

BIBLIOGRAPHY

1. M. J. Sabacky, S. M. Johnson, J. C. Martin, I. C. Paul, J. Am. Chem. Soc., 91, 7542 (1969).
2. P. Finocchiaro, D. Gust, K. Mislow, J. Am. Chem. Soc., 96, 2165 (1974).
3. A. Rieker, H. Kessler, Tetrahedron Lett., 1227 (1969).
4. D. Gust, K. Mislow, J. Am. Chem. Soc., 96, 2168 (1974).
5. J. F. Blount, P. Finocchiaro, D. Gust, K. Mislow, J. Am. Chem. Soc., 95, 7019 (1973).
6. C. Stora, Bull. Soc. Chim. Fr., 2153 (1971).
7. C. Riche, C. Pacsard-Billy, Acta Cryst. B30, 1874 (1974).
8. A. Robbins, G. A. Jeffrey, J. P. Chesick, J. Donohue, F. A. Cotton, B. A. Frenz, C. A. Murillo, Acta Cryst., B31, 2395 (1975).
9. A. H. Gomes de Mesquita, C. H. MacGillavry, K. Eriks, Acta Cryst., 18, 437 (1965).
10. P. Anderson, Acta Chem. Scand., 19, 622 (1965).
11. R. J. Kurland, I. I. Schuster, A. K. Colter, J. Am. Chem. Soc., 87, 2278 (1965).
12. I. I. Schuster, A. K. Colter, R. J. Kurland, J. Am. Chem. Soc., 90, 4679 (1968).
13. P. Finocchiaro, D. Gust, K. Mislow, J. Am. Chem. Soc., 96, 2176 (1974).
14. P. Finocchiaro, D. Gust, K. Mislow, J. Am. Chem. Soc., 96, 2165 (1974).
15. R. Breslow, L. Kaplan, D. Follette, J. Am. Chem. Soc., 90, 4056 (1968).
16. K. Mislow, D. Gust, P. Finocchiaro, R. J. Boettcher, Fortschr. Chem. Forsch., 47, 1 (1974).
17. H. Kessler, Angew. Chem. Int. Ed., 9, 219 (1970).
18. G. Binsch, Top. Stereochem., 3, 97 (1968).
19. P. Finocchiaro, D. Gust, K. Mislow, J. Am. Chem. Soc., 96, 3205 (1974).
20. P. Finocchiaro, D. Gust, K. Mislow, J. Am. Chem. Soc., 96, 3198 (1974).
21. K. Mislow, Acc. Chem. Res., 9, 26 (1976).
22. J. W. Rakshys, Jr., S. V. McKinley, H. H. Freedman, J. Am. Chem. Soc., 92, 3518 (1970).
23. J. W. Rakshys, Jr., S. V. McKinley, H. H. Freedman, J. Am. Chem. Soc., 93, 6522 (1971).
24. R. Hoffman, R. Bissell, D. Farnum, J. Phys. Chem., 73, 1789 (1969).
25. H. Kessler, A. Moosmayer, Tetrahedron, 25, 287 (1969).
26. D. Hellwinkel, M. Malan, Tetrahedron, 29, 1895 (1973).
27. R. J. Boettcher, D. Gust, K. Mislow, J. Am. Chem. Soc., 95, 7157 (1973).
28. M. G. Hutchings, C. A. Maryanoff, K. Mislow, J. Am. Chem. Soc., 95, 7158 (1973).
29. M. R. Kates, J. D. Andose, P. Finocchiaro, D. Gust, K. Mislow, J. Am. Chem. Soc., 97, 1772 (1975).
30. D. Gust, K. Mislow, J. Am. Chem. Soc., 95, 1535 (1973).

THE FORMATION AND STRUCTURE OF SELENURANES

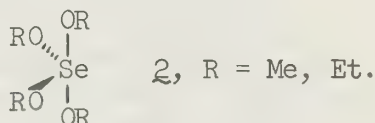
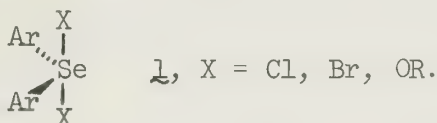
Reported by Ronald L. Amey

February 23, 1976

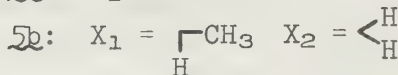
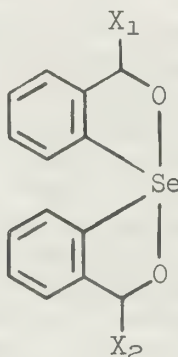
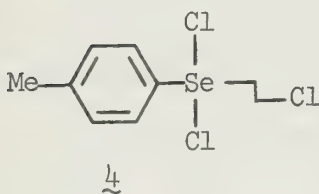
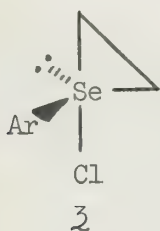
Selenuranes are a class of hypervalent compounds which contain a covalently bonded, tetracoordinate selenium(IV) atom.

The hypervalent bond, as described previously,¹ is also found in phosphoranes, sulfuranes and rare gas compounds. Essentially, the molecule forms a delocalized three-center, four-electron hypervalent bond between the central donor atom and its substituent ligands. In this case, the more electronegative atoms prefer the apical positions and incur a net formal negative charge, while the central donor atom (selenium) incurs a net formal positive charge in an overall distorted trigonal bipyramid.²

A wide variety of acyclic selenuranes have been prepared which are homologs of the selenium(IV) halides. Such species include the trialkyl(aryl)-selenuranes,³ compound 1⁴ and compound 2.⁵



Of the few monocyclic species known,⁶ 3 is the most interesting and controversial.⁷ Although the synthesis of 3 appears straightforward, attempts by Reich to reproduce the reaction resulted in 4, which was spectroscopically identical with 3 but distinct on the basis of elemental analyses.⁸ On the basis of other available data, 3 and 4 are distinct and any similarities are in fact fortuitous.



The synthesis of 5a was reported in 1914 by Lesser and Weiss.⁹ This compound was later restudied and its crystal structure was determined.¹⁰ A derivative of 5a was prepared, an optically active, partially resolved carboxylic acid, which was shown to be a distorted trigonal bipyramid whose O-Se-O bond angle of 172.4° and whose C-Se-C bond angle of 102.7° were much less than the expected angles of 180° and of 120°. In addition, a spiroselebutanolide¹² and a spiroselebutane with four carbon-selenium bonds have been prepared.¹³

A related spiro-selenurane, 5b, was shown to be optically active and isomerized to an equilibrium mixture with a $t_{1/2} = 220$ min. at 120° .¹⁴ The barrier to interconversion thus has a minimum value of 30.9 Kcal/mole.¹⁴

An important factor in the stability of the bicyclic selenuranes is the effect of the five-membered ring.¹⁴ As is expected by analogy to sulfuranes¹⁵ and phosphoranes,¹⁶ the reactivity of the selenuranes to hydrolysis follows the order: acyclic > monocyclic > bicyclic.^{5c,7a,7c,14}

BIBLIOGRAPHY

1. (a) J. I. Musher, *Angew. Chem., Int. Ed. Engl.*, 8, 54 (1969); (b) J. I. Musher, *Ann. N. Y. Acad. Sci.*, 192, 52 (1972).
2. E. L. Muetterties, W. Mahler, K. J. Packer, R. Schmutzler, *Inorg. Chem.*, 3, 1298 (1964).
3. (a) K. J. Wynne, J. W. George, *J. Am. Chem. Soc.*, 91, 1649 (1969); (b) V. Horn, R. Paetzold, *Z. Anorg. Allg. Chem.*, 398, 186 (1973).
4. (a) D. G. Foster, *J. Am. Chem. Soc.*, 55, 822 (1933); (b) K. A. Jensen, *Z. Anorg. Allg. Chem.*, 250, 245 (1943); (c) J. D. McCullough, G. Hamburger, *J. Am. Chem. Soc.*, 63, 803 (1941); (d) J. D. McCullough, G. Hamburger, *ibid.*, 64, 508 (1942); (e) J. D. McCullough, R. E. Marsh, *Acta Crystallogr.*, 3, 41 (1950); (f) R. Paetzold, U. Lindner, *Z. Anorg. Allg. Chem.*, 350, 295 (1967); (g) C. P. Smyth, A. J. Grossman, S. R. Ginsburg, *J. Am. Chem. Soc.*, 62, 192 (1940).
5. (a) V. Horn, R. Paetzold, *Z. Anorg. Allg. Chem.*, 398, 173 (1973); (b) V. Horn, R. Paetzold, *ibid.*, 398, 179 (1973); (c) R. Paetzold, M. Reichenbacher, *Z. Chem.*, 10, 307 (1970).
6. (a) M. Barlow, I. Zimmerman-Barlow, *Acta Crystallogr.*, 21, A103 (1966); (b) L. Batelle, C. Knobler, J. D. McCullough, *Inorg. Chem.*, 6, 958 (1967); (c) B. Dahlen, *Acta Crystallogr.*, B29, 595 (1973); (d) "Organic Selenium Compounds: Their Chemistry and Biology," D. H. Klayman, W. H. H. Günther, Ed., Wiley, New York, N. Y., 1973.
7. (a) D. G. Garratt, G. H. Schmid, *Can. J. Chem.*, 52, 1027 (1974); (b) D. G. Garratt, G. H. Schmid, I. G. Csizmaidia, *J. Mol. Struct.*, 22, 117 (1974); (c) D. G. Garratt, Ph.D. Thesis, University of Toronto, 1975.
8. H. J. Reich, J. E. Trend, *Can. J. Chem.*, 53, 1922 (1975).
9. R. Lesser, R. Weiss, *Chem. Ber.*, 47, 2510 (1914).
10. (a) B. Lindgren, *Acta Chem. Scand.*, 26, 2560 (1972); (b) B. Dahlen, B. Lindgren, *Acta Chem. Scand.*, 27, 2218 (1973).
11. B. Dahlen, *Acta Crystallogr.*, B30, 647 (1974).
12. L.-B. Agenäs, B. Lindgren, *Acta Chem. Scand.*, 24, 3301 (1970).
13. D. Hellwinkel, L. Fahrbach, *Justus Liebigs Ann. Chem.*, 715, 68 (1968).
14. H. J. Reich, *J. Am. Chem. Soc.*, 95, 964 (1973).
15. J. C. Martin, E. F. Perozzi, *Science*, 191, 154 (1976).
16. F. H. Westheimer, *Acc. Chem. Res.*, 1, 70 (1968).

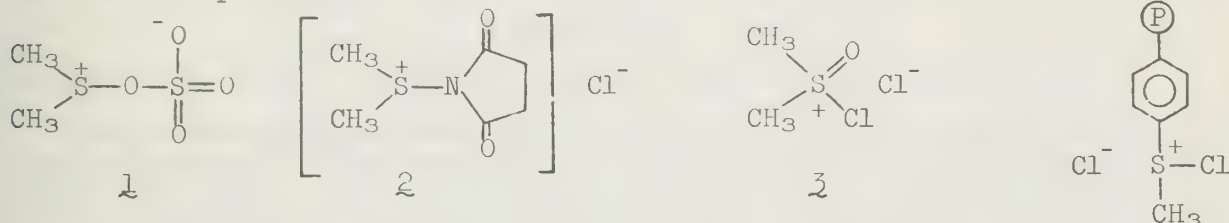
RECENT DEVELOPMENTS IN THE USE OF DIMETHYL SULFOXIDE AND RELATED REAGENTS IN OXIDATIONS

Reported by John Covington

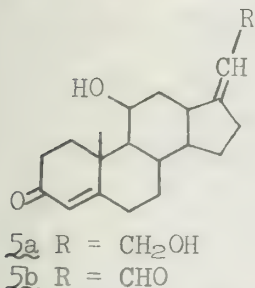
March 4, 1976

Dimethyl sulfoxide (DMSO) was first employed as an oxidizing agent in 1957, and since then a variety of organic compounds have been oxidized by DMSO.¹ Perhaps the best known method of oxidation with DMSO is the Pfitzner-Moffatt technique. This method is applicable to primary and secondary alcohol groups in a variety of compounds and the oxidation stops exclusively at the aldehyde or ketone stage. Tosylates, tertiary alcohols, olefins and amines are unaffected by the mild conditions of the Moffatt reaction, which involves the addition of the alcohol to a solution of dicyclohexylcarbodiimide (DCC) in DMSO at room temperature with phosphoric acid or pyridinium trifluoroacetate present as a proton source.¹

In recent years several modifications of the DMSO-DCC method have been developed. Among these are O-dimethylsulfoxonium sulfate, 1;² S-(N-succinimido)-dimethylsulfonium chloride, 2;⁶ dimethyl sulfoxide-chlorine complex, 3;¹⁷ and the cross-linked polymer, poly(p-methylthiostyrene)-chloride complex, 4.¹⁸ The advantages of these new reagents lie in the mildness of the reaction conditions and the ease of workup. For example, one product of the Moffatt method is N,N'-dicyclohexylurea, which has proved difficult to separate from the oxidized product.



Sulfur trioxide plus DMSO in the presence of triethylamine, which is always required, will oxidize primary and secondary alcohols to the corresponding aldehydes and ketones. The oxidations are very rapid at room temperature and usually reach completion within minutes. Perhaps the most significant feature of this reagent is its property of oxidizing allylic alcohols to α,β -unsaturated carbonyl compounds. The primary allylic hydroxyl in 11 β ,21-dihydroxy-4,17-pregnadien-3-one, 5a, was oxidized by 1 to the corresponding α,β -unsaturated aldehyde 11 β -hydroxy-4,17-pregnadien-3-on-21-al, 5b, in 70% yield. The earlier reagent DMSO-DCC showed no appreciable formation of the aldehyde 5b.²

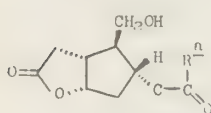
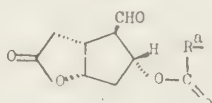


The complexes 2,^{6,9,10} and 3,¹⁷ in the presence of triethylamine, were first employed as reagents to effect the oxidation of primary and secondary alcohols by Corey and coworkers. As is clear from the examples in Table I, the yields of carbonyl compounds are remarkably high. A useful feature of these reagents is their capacity to oxidize secondary-tertiary 1,2-diols to α -hydroxy ketones without carbon-carbon bond cleavage.⁸

Unlike DMSO-SO₃, 2 and 3 will not effectively oxidize allylic alcohols. Allylic alcohols in the presence of 2 and base undergo replacement of the hydroxyl by chlorine instead of oxidation.²⁶ On the other hand, 3 reacts with olefins to form vicinal dichlorides and chlorine addition competes favorably with oxidation in attempted oxidation of allylic alcohols by 3.¹⁷

The polymeric sulfide-chlorine complex 4 offers two distinct advantages.¹⁸ The polymer is free of odor so that it is suitable for industrial operation and it can be reused after washing since it does not change chemically during

Table I. Oxidation of Alcohols with 2, 2, and 4.

Substrate	Product	Complex	Yield (%)	Reaction Time (hr)	Ref.
1-octanol	1-octanal	2	96	1	6
		3	95	2.5	17
		4	95	3	18
		2	90	1	12
		4	90	4	18
		3	98	2.5	17
benzyl alcohol	benzaldehyde	2	90	1	6
		4	66	5	18
		3	72	2	8

^aR = C₆H₅-C₆H₅(P)

reaction. The yields of aldehydes and ketones from this method, Table I, compare well to those obtained from the monomeric sulfide although the reaction times are somewhat longer.

The addition of these reagents to the list of oxidizing agents based on DMSO extends considerably the versatility of this already useful method.

BIBLIOGRAPHY

1. W. W. Epstein and F. W. Sweat, Chem. Rev., 67, 247 (1967), and references therein.
2. J. R. Parith and W. v.E. Doering, J. Am. Chem. Soc., 89, 5505 (1967).
3. E. Baggiolini, H. P. Hamlow, and K. Schaffner, J. Am. Chem. Soc., 92, 4906 (1970).
4. J. A. Marshall, and G. M. Cohen, Tetrahedron Lett., 3865 (1970).
5. T. E. Varkey, G. F. Whitfield, and D. Swern, J. Org. Chem., 39, 3265 (1974).
6. E. J. Corey and C. U. Kim, J. Am. Chem. Soc., 94, 7586 (1972).
7. J. P. McCormick, Tetrahedron Lett., 1701 (1974).
8. E. J. Corey and C. U. Kim, Tetrahedron Lett., 287 (1974).
9. E. Vilsmaier and W. Sprügel, Tetrahedron Lett., 625 (1972).
10. E. Vilsmaier and W. Sprügel, Liebigs Ann. Chem., 747, 151 (1971).
11. T. Teiter and D. Well, Tetrahedron Lett., 2249 (1975).
12. E. J. Corey and C. U. Kim, J. Org. Chem., 38, 1233 (1972).
13. H. Tanaka and S. Torii, J. Org. Chem., 40, 463 (1975).
14. G. Traverso, D. Pirillo, and A. Villa, Farmaco Ed. Sci., 28, 1040 (1973).
15. M. Lischewski and G. Adam, Tetrahedron Lett., 2569 (1975).
16. P. J. McCurry, Jr. and R. K. Singh, Tetrahedron Lett., 3325 (1973).
17. E. J. Corey and C. U. Kim, Tetrahedron Lett., 919 (1973).
18. G. A. Crosby, N. M. Weinshenker, and H. S. Uh, J. Am. Chem. Soc., 97, 2232 (1975).
19. J. D. Albright, J. Org. Chem., 39, 1977 (1974).
20. J. B. Hendrickson and S. M. Schwartzman, Tetrahedron Lett., 273 (1975).
21. W. H. Clement, T. J. Dangieri, and R. W. Tuman, Chem. Ind. (London), 755 (1969).
22. C. H. Snyder, P. L. Gendler, and H. H. Chang, Synthesis, 655 (1971).
23. V. J. Traynelis and R. Ode, J. Org. Chem., 35, 2207 (1970).
24. W. W. Epstein and J. Ollinger, Chem. Commun., 1338 (1970).
25. S. M. Ifzal and D. A. Wilson, J. Chem. Soc. C, 2169 (1969).
26. E. J. Corey, C. U. Kim, and M. Takeda, Tetrahedron Lett., 4338 (1972).
27. D. Swern, J. Am. Oil Chem. Soc., 47, 424 (1970).
28. T. M. Santosusso and D. Swern, Tetrahedron Lett., 4255 (1974).
29. R. G. Harvey and S. H. Goh, J. Am. Chem. Soc., 95, 242 (1973).
30. J. M. Ferland, Can. J. Chem., 52, 1652 (1974).

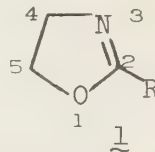
2-OXAZOLINES: USEFUL INTERMEDIATES IN ORGANIC SYNTHESIS

Reported by Patrick H. W. Lau

March 29, 1976

2-Oxazolines are five-membered heterocyclic compounds having the general formula 1. They have been known since 1884,¹ but only in recent years has their usefulness in organic synthesis been fully recognized. Numerous 2-oxazolines with a wide variety of substituents in the 2-, 4-, and 5-positions have been prepared. The 3-oxazolines and 4-oxazolines are relatively rare.^{2,3}

This abstract is concerned primarily with 2-substituted 2-oxazolines (R=alkyl or aryl), which have been shown recently to be useful precursors to aldehydes,⁴ ketones,⁵ α -substituted acetic acids and esters,⁶ substituted benzoic acids and esters,⁷ and to be powerful chiral reagents in asymmetric synthesis.⁸⁻¹⁵

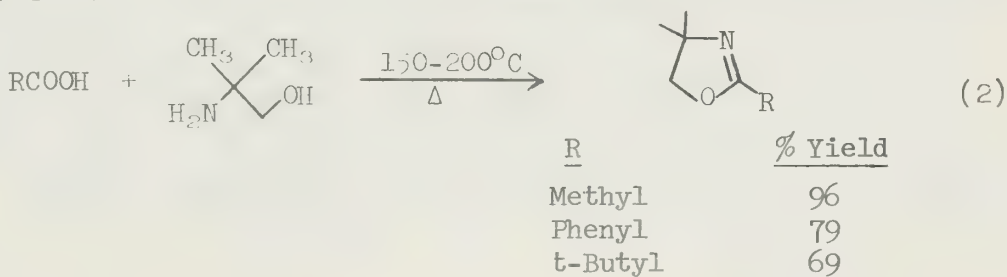
SYNTHESIS OF 2-OXAZOLINES

A). FROM N- β -HALOALKYL AMIDES. The synthesis of 2-oxazolines from N- β -haloalkyl amides has been one of the most widely used methods for preparing these reagents. The yields vary from good to excellent, depending upon the nature of substituents,² with dehydrohalogenation usually being effected by heating the β -haloalkyl amide with aqueous or alcoholic alkali (eq. 1).



N- β -Hydroxyalkyl amides can also be used. Thionyl chloride is the most commonly used cyclizing agent,¹⁶ but sulfuric acid¹⁷ and phosphorus pentoxide¹⁸ are also often employed. This route is more direct than that employing the β -haloalkyl amides, because haloalkyl amides are usually prepared from hydroxyalkyl amines. Cyclization in thionyl chloride apparently involves an $\text{S}_{\text{N}}2$ attack by the carbonyl oxygen of the amide at the β -carbon,¹⁹ as indicated by stereochemical evidence.²⁰ Another potentially useful procedure uses zinc acetate as cyclizing agent.²¹ In contrast to the thionyl chloride induced ring closure, zinc acetate-promoted cyclization gave 2-oxazolines in excellent yields with retention of configuration at the β -carbon atom. Coordination between the amide carbonyl group and the metal ion presumably induces carbonyl addition of the alcohol, which is followed by elimination.

B). FROM DIRECT CONDENSATION OF CARBOXYLIC ACIDS WITH β -HYDROXY AMINES. Another route to oxazolines involves heating an equimolar mixture of a carboxylic acid and a β -hydroxy amine, with the product being removed by direct distillation. Although this method suffers a disadvantage when the oxazoline cannot be distilled out of the reaction mixture, it represents the simplest and most inexpensive process for generating 2-oxazolines. A series of 2-alkyl and 2-aryl substituted 2-oxazolines has been prepared in yields ranging from 69 to 96% (eq. 2).²²

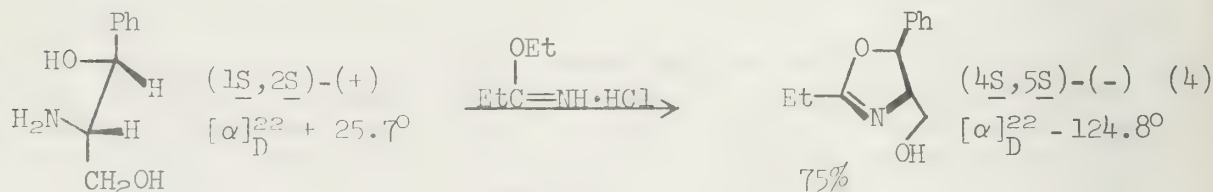


C). FROM AZIRIDINES. Thermal,²³ acidic,²⁴ or iodide ion-assisted²⁵ rearrangement of N-acyl aziridines to 2-oxazolines is a well-known process. The acyl aziridines are readily prepared quantitatively from carboxylic acids and aziridines in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC), or from their acid chlorides and aziridines in the presence of a base (eq. 3).



Thermal rearrangement usually gives a mixture of products and is, therefore, not suitable for preparative work. Iodide ion-catalyzed isomerization has been shown to be stereoselective, the selectivity being greater with trans- than with cis-aziridines. Acidic rearrangement is usually carried out in 80 to 96% sulfuric acid and the free base can be liberated with an appropriate amount of strong base.

D). FROM IMINO ETHERS. Bockemühl and Knoll²⁶ found that 2-oxazolines can be obtained by heating α -iminoalkyl ether hydrochlorides with β -hydroxy amines. Retention of configuration at both carbons has been demonstrated by Johnson.²⁰ This method provides a very useful approach to chiral oxazolines for asymmetric synthesis when optically active β -hydroxy amines are employed (eq. 4).⁸



CHEMICAL PROPERTIES OF 2-OXAZOLINES

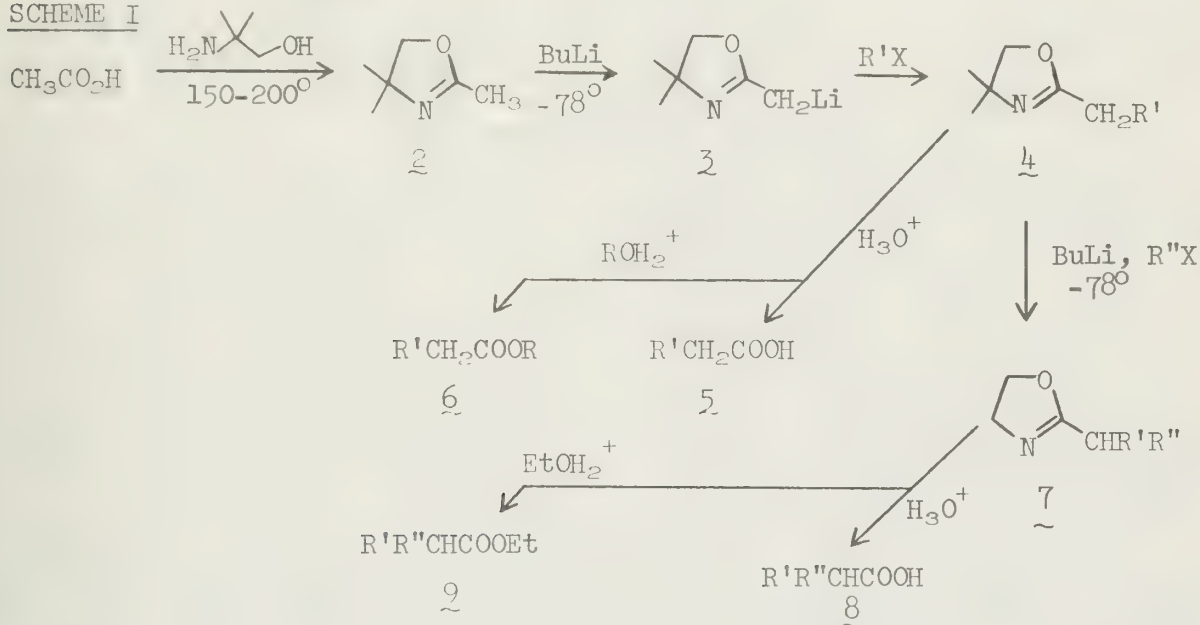
2-Oxazolines are typical weak bases which form salts with acids and quaternary compounds with alkyl halides. They are quite stable in cold acids and bases, but can be completely hydrolyzed by heating with dilute acids. Basic hydrolysis is also possible but only under more vigorous conditions. Because of the electron withdrawing C-N group α -hydrogens of the 2-alkyl group are acidic and are readily abstracted by strong bases such as butyllithium and lithium diisopropylamide (LDA).

The oxazoline ring itself possesses unusual stability toward many oxidizing and reducing agents. Billman and Parker²⁷ reported that 2-phenyl-4,4-bis-(hydroxymethyl)-2-oxazoline could be oxidized to the corresponding oxazoline-4,4-dicarboxylic acid with alkaline permanganate at 40°C. Similarly, Adams and Leffler¹⁷ successfully nitrated 2-phenyl-2-oxazoline to 2-(*m*-nitrophenyl)-2-oxazoline in 64% yield with a nitric acid-sulfuric acid mixture below 10°C. The nitro compound was subsequently reduced to the amino derivative with iron and hydrochloric acid without cleaving the ring. 2-Oxazolines are also inert to Grignard reagents and lithium aluminum hydride, as will be indicated below.

SYNTHETIC APPLICATIONS

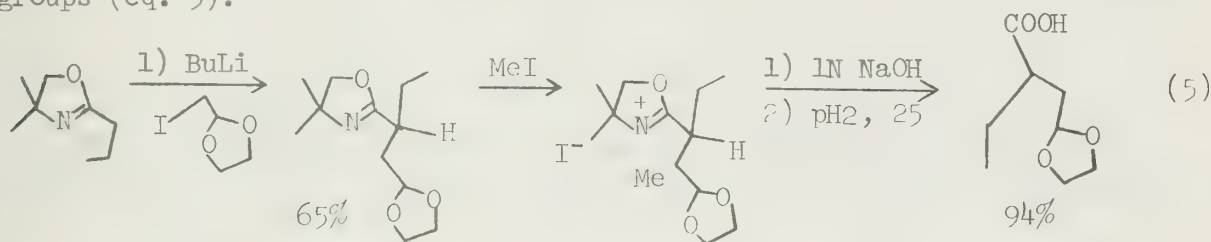
1). SIDE-CHAIN ALKYLATION. In 1970 Meyers and coworkers⁶ reported that 2,4,4-trimethyl-2-oxazoline (2) is a useful precursor to homologated acetic acids and esters (Scheme I).

SCHEME I



Further alkylation of 7 failed under the reaction conditions. Various mono- and dialkyl substituted acetic acids, 5 and 8, and esters, 6 and 9, were prepared. Their yields and those obtained by malonic ester synthesis are compared in Table I.

Cleavage to carboxylic acids 5 or 8 can also be performed under alkaline conditions if the elaborated oxazoline carriers acid-sensitive groups (eq. 5).



Similarly, alkylation of the anion 4a with epoxides at low temperature affords compounds (10), which upon acidic hydrolysis give a variety of γ -butyrolactones (11) with alkyl substituents in the α , β , and/or γ positions.²⁸ 1,2-Disubstituted epoxides are quite resistant to alkylation. The main controlling factors were suggested to be the steric environment of the epoxide carbons and the steric bulk of R' on 4a.

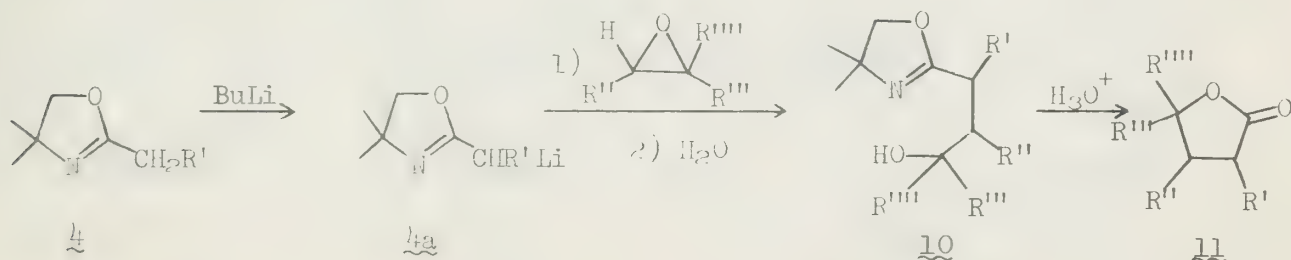


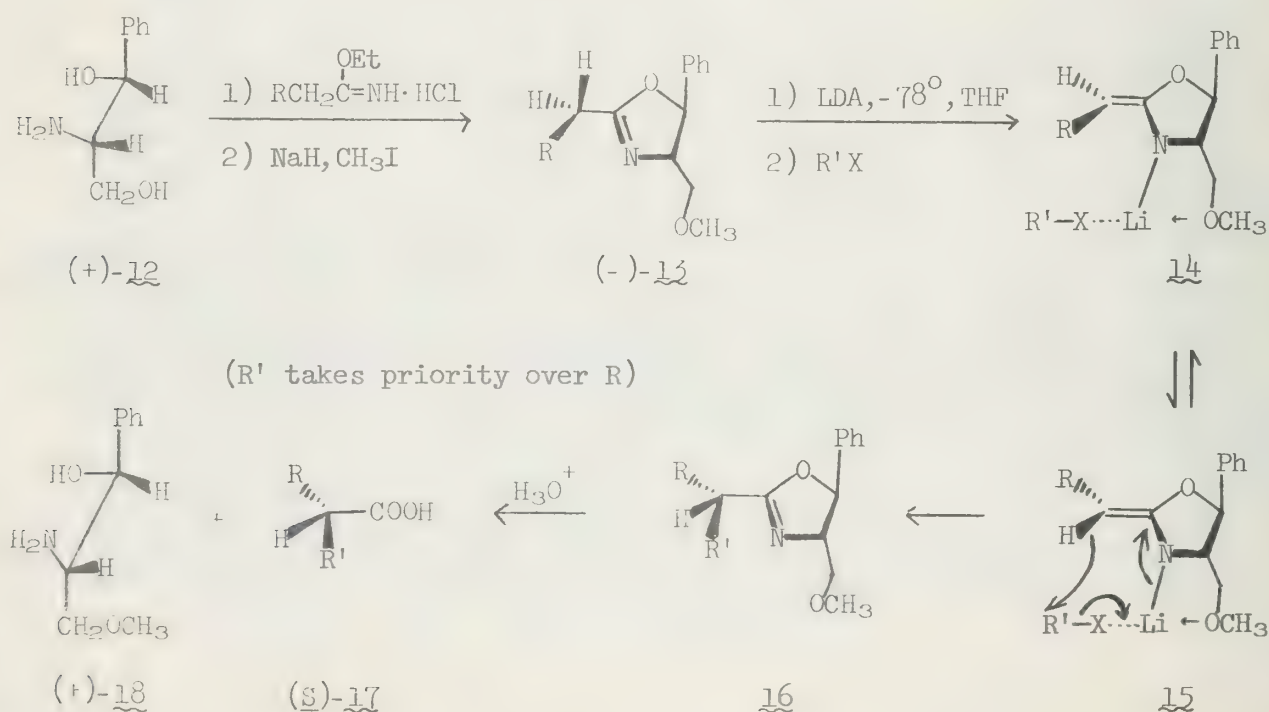
Table I.

R'X	R''X	% ^a ₂	% ^a ₆ (R)	% ^b ₈	% ^b ₉	R'CH(CO ₂ Et) ₂ ^c	R'R''C(CO ₂ Et) ₂ ^c
<u>n</u> -BuBr		80	84(Et)			80-90	
C ₆ H ₅ CH ₂ Cl		95	98(Et) 95(Me) 99(<u>i</u> -Pr) 85(<u>sec</u> -Bu) 0.5(<u>t</u> -Bu)			85	
CH ₂ -CBrCH ₂ Br			86(Et)			---	
CH ₂ =CHCH ₂ Cl		77	96(Et) 95(<u>i</u> -Pr)			91(X=Br)	
CH ₂ -C(CH ₂) ₃ I CH ₃			94(Et)			---	
C ₆ H ₅ CH ₂ I	CH ₃ I			89	80		63-80
C ₆ H ₅ CH ₂ I	CH ₂ =CHCH ₂ Cl			84	88		-----
C ₆ H ₅ CH ₂ I	<u>n</u> -BuBr			77	83		70

^a-Yields of 5 and 6 were based on 2. ^b-Yields of 8 and 9 were based on 4. ^c-Data taken from A. C. Cope, et al., Org. Reactions, 9, 107 (1957).

2). ASYMMETRIC SIDE-CHAIN ALKYLATION. The potential exists for an optically active oxazoline which would provide an asymmetric environment for side-chain alkylation and eventually lead to optically active acids or esters. The following sequence bears out this prediction (Scheme II).

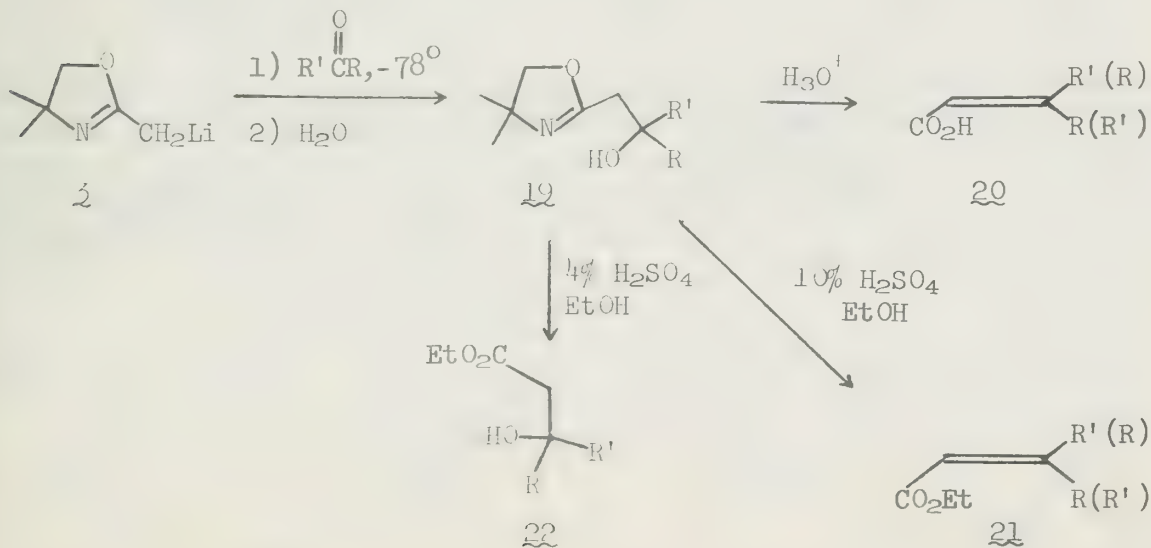
SCHEME II



Chiral oxazoline $(-)-\underline{11}$ (whose maximum rotation is not known) can be prepared in 68% yield ($R=CH_3$) by condensation of the commercially available (Strem Chemical, Inc., Danvers, Mass.) $(1S, 2S)-(+)-1$ -phenyl-2-amino-1,3-propanediol ($\underline{12}$) with an α -imino ether. Various $(S)-2$ -methylalkanoic acids ($\underline{17}$) were obtained in yields ranging from 68-72% with optical purity of 60-70%. The amino alcohol $(+)-\underline{18}$ was recovered in 80-90% yield without racemization and could be recycled for further synthesis to $(-)-\underline{13}$. In a similar fashion the enantiomeric $(-)-\underline{12}$ amino diol gave $(R)-\underline{17}$ in comparable yields and optical purities. The order of alkyl group introduction was found to be critical to the success of the asymmetric synthesis when methyl iodide was used but apparently had no effect on bulkier alkylating agents such as methyl sulfate or tosylate. For example, alkylation of $(-)-\underline{13}$ ($R=CH_3$) with benzyl iodide gave $(S)-2$ -methyl-3-phenylpropionic acid in 70% optical purity. However, alkylation of $(-)-\underline{13}$ ($R=CH_2C_6H_5$) with methyl iodide and methyl sulfate (or tosylate) afforded $(R)-2$ -methyl-3-phenylpropionic acid in 1% and 63% optical yields, respectively. These results could be rationalized as follows: Proton removal from $\underline{13}$ gives rise to the two isomeric lithio salts $\underline{14}$ and $\underline{15}$ which are interchangeable. Attack by the electrophile is assumed to occur from the bottomside since a topside approach would be difficult to explain the profound effect of methyl sulfate (or tosylate) versus methyl iodide. However, the topside approach cannot be definitely ruled out. Alkylation on $\underline{15}$ is energetically more favorable because of lesser steric interaction between the R and R' groups. The lithium cation forms a bulkier complex ($\underline{15}$) with the oxygen atoms of methyl sulfate (or tosylate) than that with methyl iodide which further widens the relative rates of attack on $\underline{14}$ and $\underline{15}$ and results in greater stereoselectivity. A marked increase in stereochemical efficiency of the process with decreasing temperatures has also been observed.

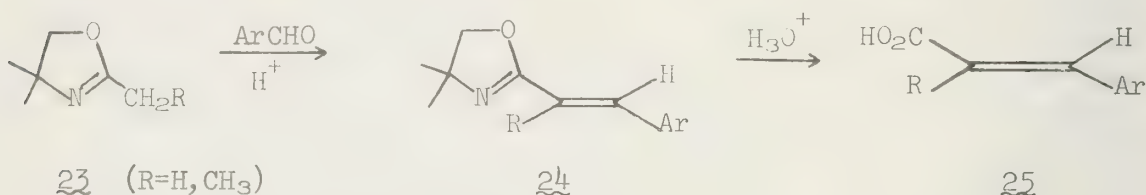
The potential of chiral oxazolines in synthesis of chiral molecules has been further demonstrated by Meyers. Treatment of the lithio salt of $(-)-\underline{13}$ ($R=H$) with epoxides and subsequent conversion of the corresponding alkoxide to its trimethylsilyl derivative followed by further α -alkylation produced a series of $(R)-2$ -substituted γ -butyrolactones in 64-73% optical yield after acidic hydrolysis. Reversal of the order of introduction of substituents would be expected to give the (S) -enantiomers.¹⁵

3). CONDENSATION. Reaction of the lithio salt of $(-)-\underline{13}$ ($R=H$) with carbonyl compounds was also reported by Meyers; however, the enantiomeric purity was only 18-25%.¹⁰



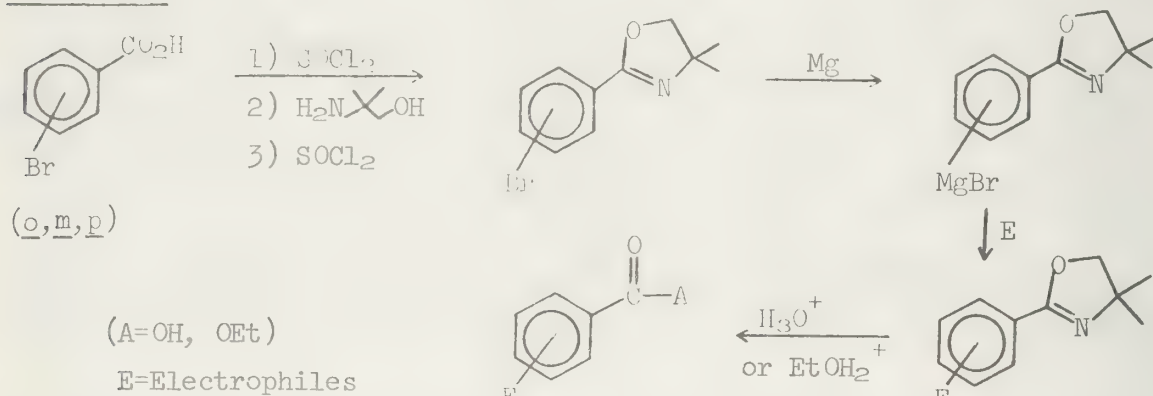
The anion **3** was found to react with a variety of carbonyl compounds,^{6b} affording adducts (**19**) in high yields. Acidic hydrolysis under different conditions furnished the unsaturated acids, **20**, unsaturated esters, **21**, or β -hydroxy esters, **22**. A thermodynamic mixture of α,β - and β,γ -unsaturated isomers of the unsaturated acids and esters were obtained. When the 2-alkyl substituent was larger than methyl, yields of all three products were substantially lower. The main products were the starting carbonyl compounds and carboxylic acids, presumably through facile reversion of the α -alkyl- β -hydroxy acids and esters to their precursors under the reaction conditions.^{29,30}

In 1962, Wehrmeister³¹ reported that 2-methyl- and 2-ethyl-2-oxazolines (**23**) condense efficiently with aromatic aldehydes in the presence of acidic catalysts, yielding adducts (**24**), which upon acidic hydrolysis provided the trans-cinnamic acids (**25**) in good yields. This approach to cinnamic acids may be compared with the classical Perkin, Doebner, or Wittig methods.

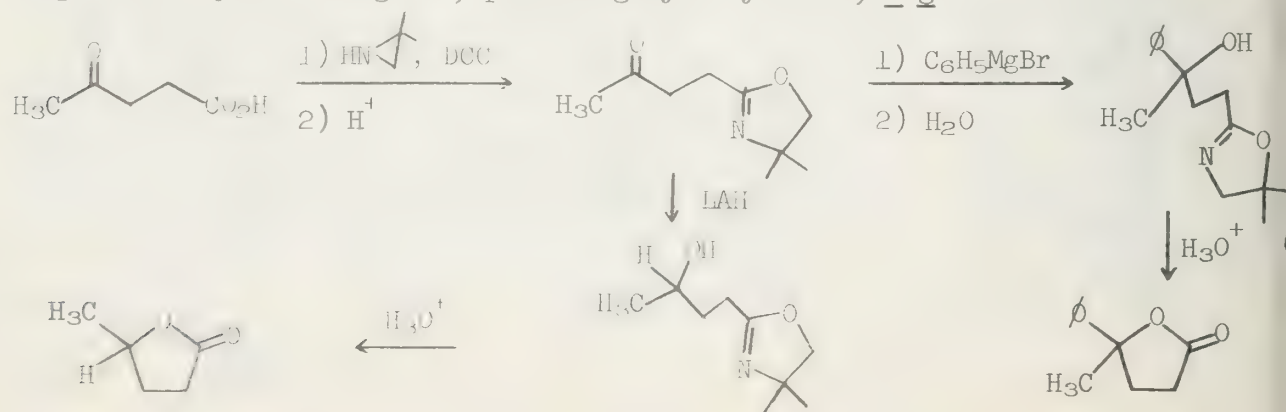


4). PROTECTION OF CARBOXYL. The oxazoline ring is an excellent and simple carboxyl protecting group which does not react with Grignard or lithium aluminum hydride reagents.^{7a,b} A series of substituted benzoic acids, using the Grignard reagents from their o-, m-, or p-bromo derivatives, was prepared while the carboxyl groups were masked as the oxazolines (Scheme III).

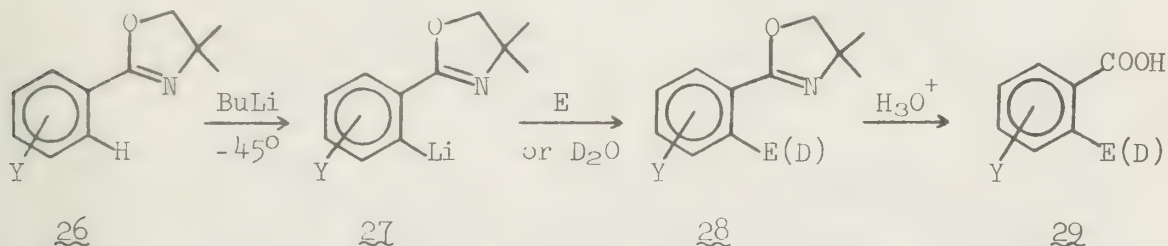
SCHEME III



Furthermore, keto-containing oxazoline derivatives can be treated with Grignard or hydride reagents, producing hydroxy acids, e.g.

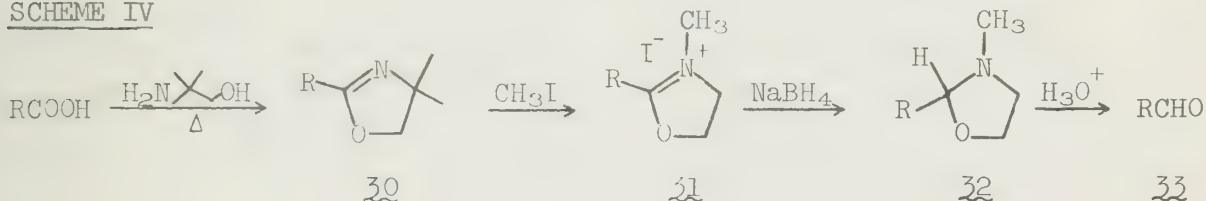


5). AROMATIC METALATION. Polydeuterated and polysubstituted benzoic acids have been synthesized by regioselective ortho-metalation of 2-aryl oxazolines. 2-Aryl oxazolines (26) undergo metalation predominantly in the ortho position. Coordination of the lithium base with the adjacent lone pair on oxygen or nitrogen followed by exchange with the ortho proton has been proposed as a possible mechanism in other similar systems such as anisole and benzamides, respectively.³²



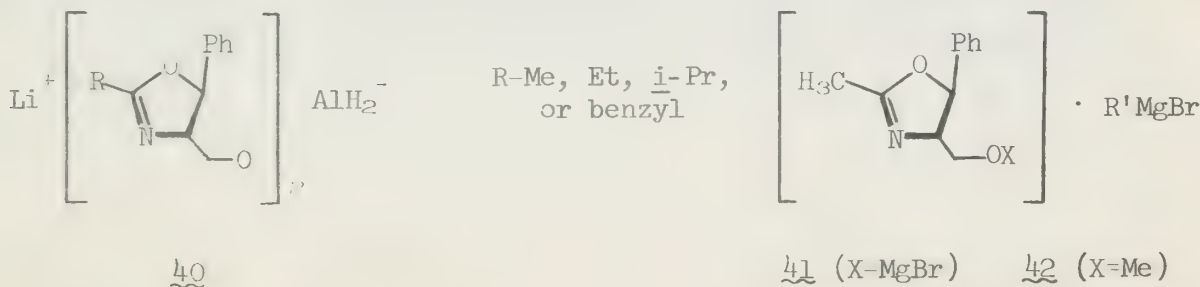
6). ALDEHYDE SYNTHESIS. Reduction of carboxylic acids with hydride reagents usually provides alcohols.³³ Nordin^{4a} reported in 1966 that carboxylic acids can be reduced to the corresponding aldehydes through the 2-oxazoline intermediates. Conversion to the highly electrophilic quaternary salt 31 is necessary before treatment with alcoholic sodium borohydride, since the oxazoline 30 is quite stable to hydride reduction, as shown before. Acidic hydrolysis of the oxazolidine 32 generates the aldehyde 33 in good yield (Scheme IV).

SCHEME IV

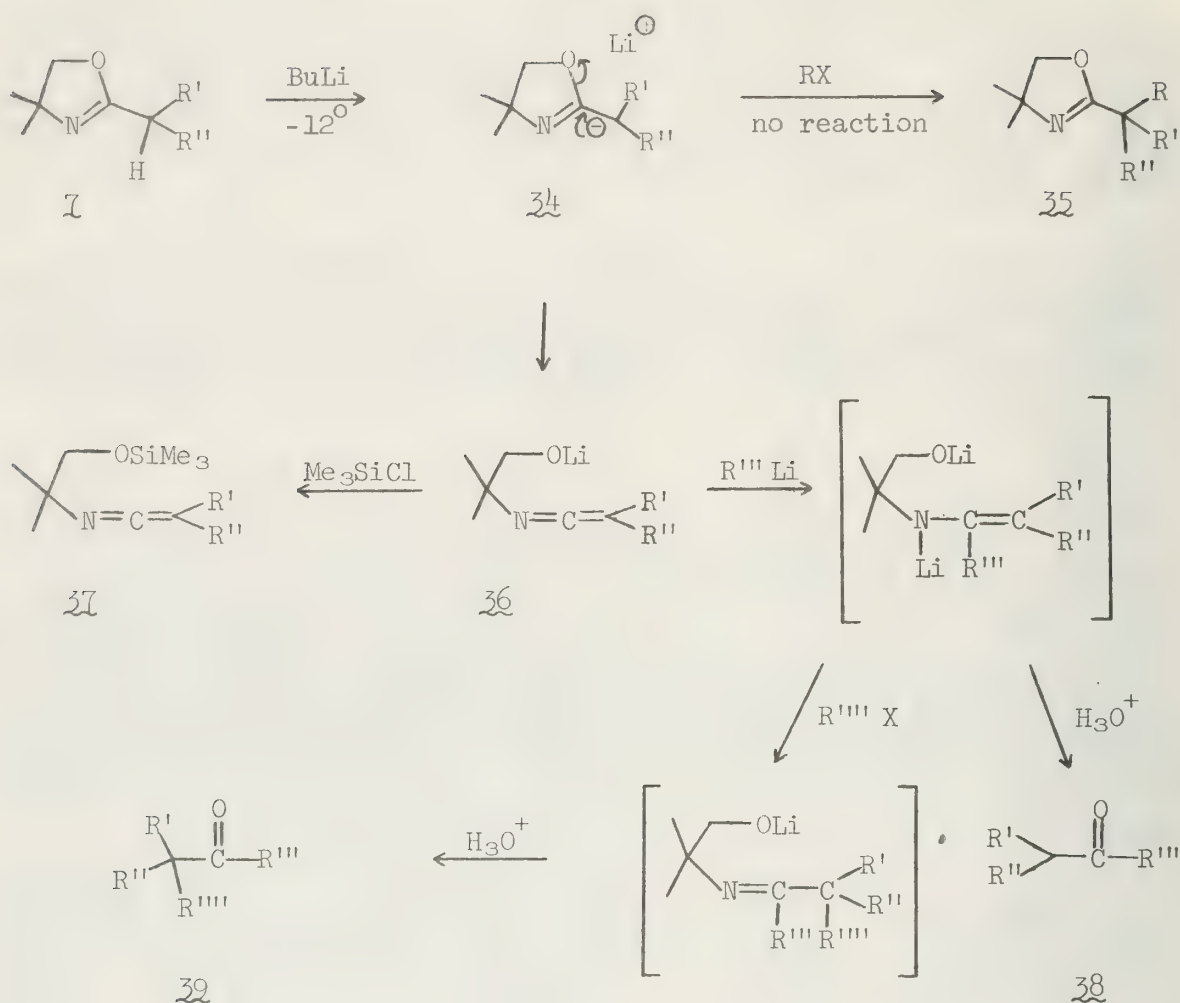


7). KETONE SYNTHESIS. Attempts to alkylate 7 to 35 were unsuccessful due to the instability of the anion 34 under the reaction conditions. Rapid rearrangement of 34 to the ketenimine 36 was demonstrated by trapping it as its trimethylsilyl derivative, 37. The ketenimine 36 can serve as a precursor to ketones as shown by Dubois and Lion⁵ in Scheme V. A variety of α,α -disubstituted and α,α,α -trisubstituted ketones, 38 and 39 respectively, have been prepared by this process in satisfactory yields.

8). CHIRAL REAGENTS. Reduction of ketones with chiral oxazoline-hydride reagent 40 gives secondary alcohols with varying degrees of enantiomeric excess.¹¹ Chiral oxazoline-Grignard reagents of the type 41 and 42 have also been made, but the optical yields of the product alcohols were lower than satisfactory.¹²



SCHEME V



SUMMARY

The ease of formation and cleavage of the oxazoline ring, coupled with its remarkable stability against many oxidizing, reducing, Grignard, and hydride reagents, provides an excellent and simple system for masking carboxyl groups.

The quantitative formation of 2,4,4-trimethyl-2-oxazoline from its readily available starting materials suggests it may serve as an alternative to the classical approaches to mono- and dialkylated acetic acids and esters via the malonic or acetoacetic ester procedures. Asymmetric synthesis employing the chiral oxazoline 13 also appears promising. However, since the maximum rotation of the chiral oxazoline 13 is not known, the optical yields of the various products reported in this abstract probably represent only the minimum values achievable today. More refined experimental technique will undoubtedly improve the efficiency of the process in the future.

REFERENCES

1. R. Andreasch, *Monatsh. Chem.*, 5, 33 (1884).
2. R. H. Wiley and L. L. Bennett, Jr., *Chem. Rev.*, 44, 447 (1949).
3. J. A. Frump, *ibid.*, 71, 483 (1971).
4. (a) I. C. Nordin, *J. Heterocycl. Chem.*, 3, 531 (1966); (b) A. I. Meyers and E. W. Collington, *J. Am. Chem. Soc.*, 92, 6676 (1970).
5. C. Lion and J. E. Dubois, *Tetrahedron*, 29, 3417 (1973).
6. (a) A. I. Meyers and D. L. Temple, *J. Am. Chem. Soc.*, 92, 6644 (1970); (b) A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, *J. Org. Chem.*, 39, 2778 (1974).
7. (a) A. I. Meyers and D. L. Temple, Jr., *J. Am. Chem. Soc.*, 92, 6646 (1970); (b) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, 39, 2787 (1974); (c) A. I. Meyers and E. D. Mihelich, *ibid.*, 40, 3158 (1975); (d) A. I. Meyers and E. D. Mihelich, *J. Am. Chem. Soc.*, 97, 7383 (1975); (e) H. W. Gschwend and Hamdan, *J. Org. Chem.*, 40, 2008 (1975).
8. A. I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc.*, 96, 268 (1974).
9. A. I. Meyers and K. Kamata, *J. Org. Chem.*, 39, 1603 (1974).
10. A. I. Meyers and G. Knaus, *Tetrahedron Lett.*, 1333 (1974).
11. A. I. Meyers and P. M. Kendall, *ibid.*, 1337 (1974).
12. A. I. Meyers and M. E. Ford, *ibid.*, 1341 (1974).
13. A. I. Meyers, G. Knaus, and P. M. Kendall, *ibid.*, 3495 (1974).
14. A. I. Meyers and G. Knaus, *J. Am. Chem. Soc.*, 96, 6508 (1974).
15. A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, 40, 1186 (1975).
16. M. Bergmann and E. Brand, *Ber.*, 56, 1280 (1923).
17. M. T. Leffler and R. Adams, *J. Am. Chem. Soc.*, 59, 2252 (1937).
18. H. Wenker, *ibid.*, 57, 1079 (1935).
19. J. W. Cornforth, in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, 1957, pp 377-390.
20. W. S. Johnson and E. N. Schubert, *J. Am. Chem. Soc.*, 72, 2187 (1950).
21. E. Ghera and S. Shoua, *Chem. Comm.*, 639 (1972).
22. P. Allen, Jr., and J. Ginos, *J. Org. Chem.*, 28, 2759 (1963).
23. I. J. Burnstein, P. E. Fanta, and B. S. Green, *ibid.*, 35, 4084 (1970).
24. C. U. Pittman and S. P. McManus, *ibid.*, 35, 1187 (1970).
25. T. A. Foglia, L. M. Gregory, and G. Maerckel, *ibid.*, 35, 3779 (1970).
26. M. Bockemühl and R. Knoll, U. S. patent 1,958,529 (May 15, 1934).
27. J. H. Billman and E. E. Parker, *J. Am. Chem. Soc.*, 67, 1069 (1945).
28. A. I. Meyers, E. D. Mihelich, and R. L. Nolen, *J. Org. Chem.*, 39, 2783 (1974).
29. W. Adam, J. Baeza, and C. U. Liu, *J. Am. Chem. Soc.*, 94, 2000 (1972).
30. R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, 41, 1662 (1963).
31. H. L. Wehrmeister, *J. Org. Chem.* 27, 4418 (1962).
32. B. J. Wakefield, "The Chemistry of Organolithium Compounds," Pergamon Press, Elmsford, N.Y., 1974, Chapter 3.
33. H. O. House, "Modern Synthetic Reactions," 2nd Ed., W. A. Benjamin, Inc., 1972, Chapter 2.

TERPENOID ANTIMICROBIAL AGENTS FROM MARINE SOURCES

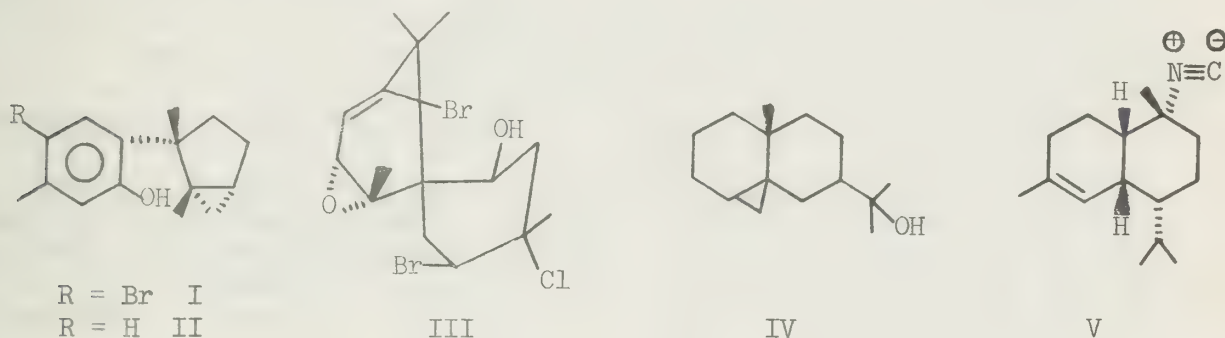
Reported by Yang M. Goo

April 5, 1976

Recent progress in the field of marine natural products has revealed many interesting bioactive substances. Although the use of marine organisms for medical purposes was described a long time ago in the Orient, a serious effort to understand the chemistry of bioactive substances from the oceans began only about ten years ago. During the last decade numerous reviews have emphasized the potential of the sea to provide biomedically useful substances.¹⁻⁴ The present report limits itself to more recent work dealing with terpenoid antimicrobial substances isolated from the marine environment, mainly from marine algae and sponges.

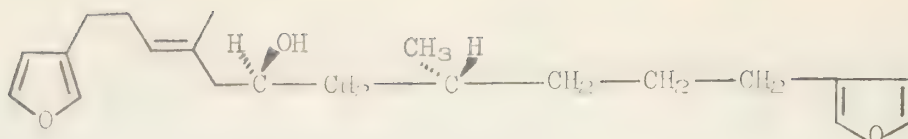
Algae

Although marine algae have been known for a long time to contain antimicrobial agents,^{2,3} isolation of these constituents began only in 1960. Along with numerous brominated phenols, a total of about 60 halogenated terpenes are now known.⁵⁻⁹ Most of them are generally regarded to be biosynthesized via bromonium ion-induced cyclization.¹⁰⁻¹³ Recently, laurinterol (I) and debromolaurinterol (II) have been found to be important antimicrobial principles in many marine algae.¹⁴ They were first isolated from *Laurencia intermedia* but have been shown to be distributed widely in *Laurencia* sp. Sims, et al., have also reported that other terpenes, pre-pacifenol (III) and cycloeuodesmol (IV), isolated from marine algae,^{14,15} have antimicrobial properties.

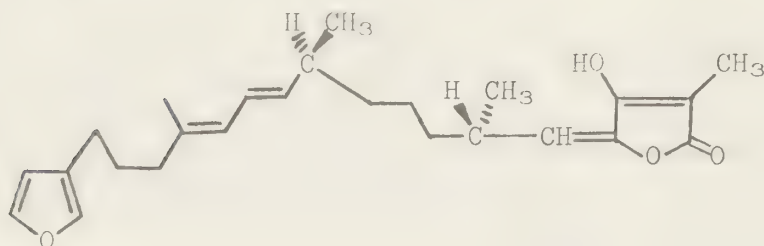


Sponges

Following the initial observation by Nigrelli that marine sponges exhibit antimicrobial activity, surveys indicated 10-35% of marine sponges tested had inhibitory effect on bacteria, fungi, viruses or tumors.⁴ Brominated tyrosine metabolites have been identified as the principal antimicrobial compounds in marine sponges,¹⁶ but recently some terpenes-- an isonitrile (V),¹⁷ furospongins-1 (VI),¹⁸ variabilin¹⁹ and strobilinin²⁰-- have also been reported to have antibacterial properties. Until the recent isolation of isonitriles from an *Axinella* sp.²¹ and a *Halichondria* sp.,¹⁷ the only known isonitrile compound was xanthocillin, isolated from *Penicillium notatum*.²² Minale and his group have identified several furanoid terpenes, which can be classified into three groups: 1) sesquiterpenes, 2) compounds having 21 carbon atoms [including furospongins-1 (VI)] and 3) sesterterpenes [including variabilin, strobilinin and fasciculatin (VII)²³] characterized by a tetronic acid moiety. Presently there are 21 marine natural products in the first group, 6 in the second, and 7 in the third.



VI



VII

Other Organisms

As early as 1960, crassin acetate and eunicin were reported as antimicrobial principles in some gorgonians.¹ Crassin acetate has recently been reported to have antitumor properties as well.²⁴ Antifungal steroids in sea cucumbers have long been known, and recently the total structure of holotoxin, an antifungal principle in sea cucumbers, was reported.²⁵

BIBLIOGRAPHY

1. P. J. Scheuer, "Chemistry of Marine Natural Products", 1973, Academic Press, N. Y.
2. M. H. Baslow, "Marine Pharmacology, 1969", The Williams and Wilkins Co., Baltimore.
3. A. der Marderosian, J. Pharm. Sci., 58, 1 (1969).
4. P. R. Burkholder, Lloydia, 32, 466 (1969).
5. J. F. Siuda and F. J. DeBernardis, Lloydia, 36, 107 (1973).
6. W. Fenical, J. Phycol., 11, 245 (1975).
7. A. G. Gonzalez, J. M. Auiar, J. D. Martin and M. Norte, Tetrahedron Lett., 2499 (1975).
8. M. Suzuki, E. Kurosawa and T. Irie, Tetrahedron Lett., 821 (1974).
9. S. M. Waraszkiewicz and K. L. Erickson, Tetrahedron Lett., 3571 (1974).
10. E. E. van Tamelen and T. J. Curphey, Tetrahedron Lett., 121 (1962).
11. V. Calo, L. Lopez, G. Pesce and P. E. Todesco, Tetrahedron, 29, 1625 (1973).
12. A. G. Gonzalez, J. D. Martin, C. Perez and M. A. Ramirez, Tetrahedron Lett., 137 (1976).
13. T. Kato, I. Ichinose, S. Kumazawa and Y. Kitahara, Bioorg. Chem., 4, 188 (1975).
14. J. J. Sims, M. S. Donnel, J. V. Leary and G. H. Lacy, Antimicrob. Agents Chemother., 7, 320 (1975).
15. W. Fenical and J. J. Sims, Tetrahedron Lett., 1137 (1974).
16. G. E. Krejcarek, R. H. White, L. P. Hager, W. O. McClure, R. D. Johnson, K. L. Rinehart, Jr., J. A. McMillan and I. C. Paul, Tetrahedron Lett., 507 (1975).
17. B. J. Burrenson, C. Christophersen and P. J. Scheuer, Tetrahedron, 31, 2015 (1975).
18. G. Cimino, S. De Stefano and L. Minale, Tetrahedron, 27, 4673 (1971).
19. D. J. Faulkner, Tetrahedron Lett., 3821 (1973).
20. I. Rothberg and P. Shubiak, Tetrahedron Lett., 769 (1975).
21. E. Fattorusso, S. Magno, L. Mayol, C. Santacroce and D. Sica, Tetrahedron, 30, 3911 (1974).
22. I. Hegedorn and H. Tonjes, Pharmazie, 12, 567 (1957); Chem. Abstr., 52, 6362c (1958).
23. C. Carieri, E. Fattorusso, C. Santacroce and L. Minale, Tetrahedron, 28, 267 (1972).
24. A. J. Weinheimer and J. A. Matson, Lloydia, 38, 378 (1975).
25. I. Kitagawa, T. Sugawara and I. Yosioka, Tetrahedron Lett., 4111 (1974).

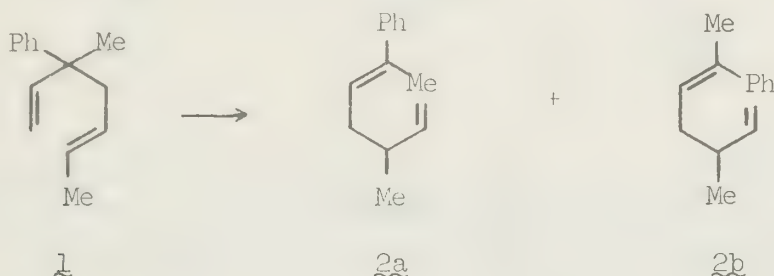
SELF-IMMOLATIVE ASYMMETRIC SYNTHESIS:
TRANSFER OF CHIRALITY IN [2,3] SIGMATROPIC REARRANGEMENTS

Reported by Reginald A. Booker

April 8, 1976

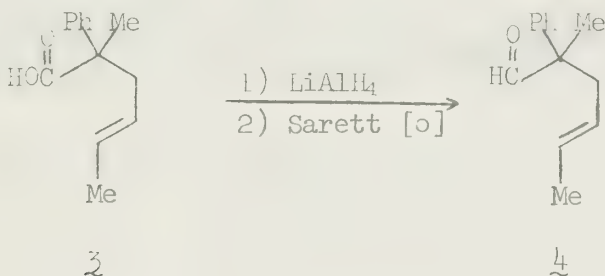
The [3,3] sigmatropic rearrangements have been known to proceed by an electron reorganization via a concerted, cyclic process. In 1967 in a study of asymmetric induction in the Cope rearrangement, Hill reported 3-methyl-3-phenyl-trans-1,5-heptadiene (1) rearranged quantitatively at 250° to an 87:13 mixture of cis- and trans-3-methyl-6-phenyl-1,5-heptadienes (2a and 2b).⁴⁶ See Scheme I. The structures of 2a and 2b were in accord with their infrared, nmr, and ultraviolet spectra, the double bond being established by the ultraviolet spectra;⁴⁷ 2a, λ_{\max} 249 nm (log ϵ 4.09); 2b, λ_{\max} 235 nm (log ϵ 3.78).⁴⁶

Scheme I



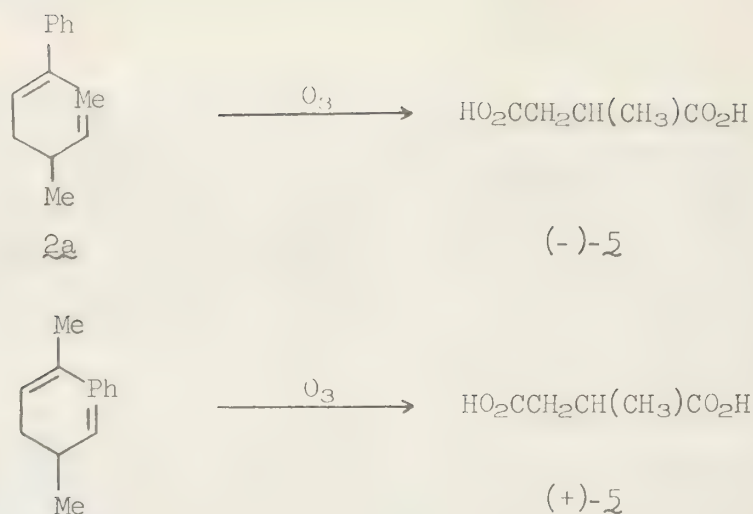
Optically active 1 was prepared by resolution of acid 3 with dehydroabietylamine, conversion of 3, $[\alpha]_D^{22} + 40.3^\circ$, into (+)-4 by lithium aluminum hydride reduction followed by oxidation with Sarett's reagent, and use of (+)-4 in the Wittig synthesis (Scheme II). The absolute configuration of (+)-3 was established by ozonolysis to (+)-2-methyl-2-phenylsuccinic acid, which was then independently related to (R)-(-)-2-methyl-2-phenylbutyric acid. The absolute configuration and maximum rotation of the (R)-(-)-2-methyl-2-phenylbutyric acid are known.⁴⁸ Thus, the sequence of correlations showed that 1, $[\alpha]_D^{22} + 13.7^\circ$, had the (R)-configuration and an optical purity of 95%.⁴⁶

Scheme II



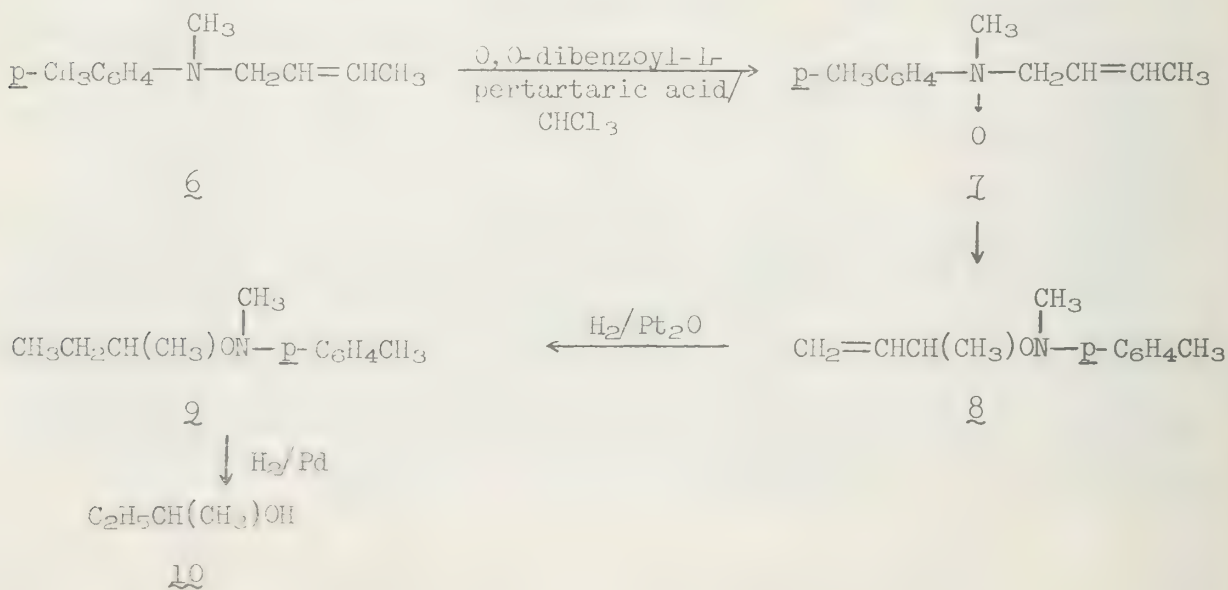
Hill reported that Cope rearrangement of (R)-(+)-1 gave 2a and 2b, which proved to be optically active. Ozonolysis of 2a, $[\alpha]_D^{22} + 8.27^\circ$, afforded (S)-(-)-methylsuccinic acid (5), $[\alpha]_D^{22} - 14.1^\circ$, while ozonolysis of 2b, $[\alpha]_D^{22} + 14.9^\circ$, led to (R)-(+)-methylsuccinic acid, (+)-5, $[\alpha]_D^{22} + 13.8^\circ$ (Scheme III), showing that (+)-2a and (+)-2b have opposite configurations at the new asymmetric center as well as at the double bond. Based on the maximum rotation of methylsuccinic acid, 2a and 2b are formed in optical purities of 91 and 89%, which corresponds to an optical yield of 94-96% in the Cope rearrangement.⁴⁶

Scheme III

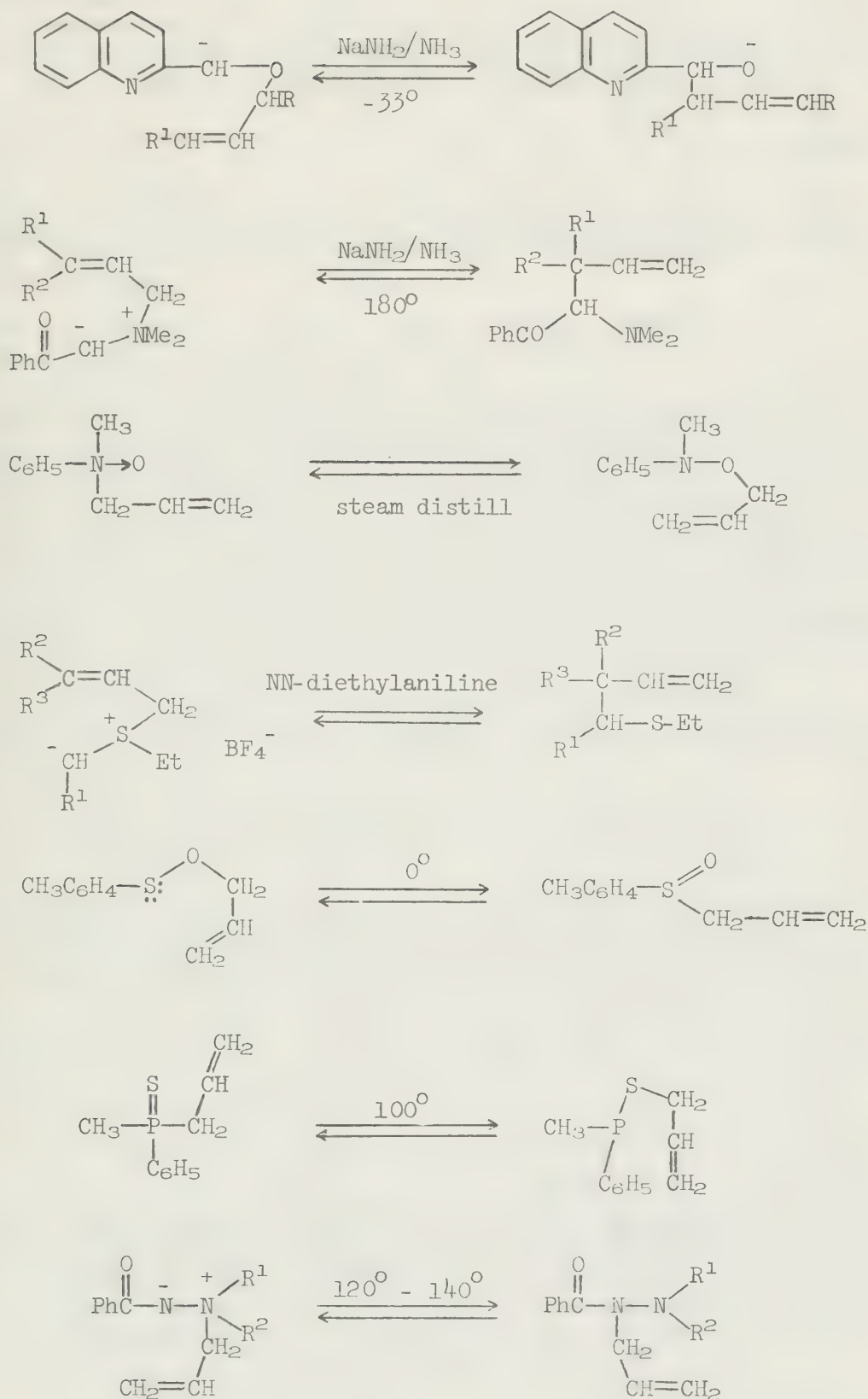


After 10 years of study on [3,3] sigmatropic rearrangements, attention has turned to proving the stereochemical nature of [2,3] sigmatropic rearrangements. As suggested by Inouye, the [2,3] sigmatropic rearrangements are the anionic equivalent of the Cope [3,3] rearrangement.¹⁴ These [2,3] shifts involve a variety of systems other than the carbon system.¹ These include the Wittig,²⁻⁷ Stevens,⁸ and Meisenheimer⁹⁻¹³ rearrangements of allylic systems, as well as the rearrangements of allylic sulfonium ylides,^{4,15-27} sulfenates,^{4,28-29} phosphinates,³⁰⁻³¹ amidammonium salts,³² and other hetero atoms.³³⁻³⁷ See Scheme IV (next page).

Inouye used (R)-(+)-N-trans-methyl-p-toluidine oxide (7) to derive unambiguous stereochemical evidence supporting the concerted nature of the [2,3] sigmatropic rearrangements. Compound 7 was prepared from the parent amine (6) by oxidation with O,O-dibenzoyl-L-pertartaric acid in chilled chloroform. Reaction of (+)-7 in refluxing 10% aqueous sodium hydroxide for 30 min gave (+)-O-(α -methylallyl)-N-methyl-p-tolylhydroxylamine, [8, $[\alpha]_D + 2.42^\circ$ (c 1.25, chloroform)], in 90% yield, indicating a [2,3] allylic shift. The absolute configuration of compound 8 was correlated by its conversion to (S)-2-butanol (10). Catalytic hydrogenation of

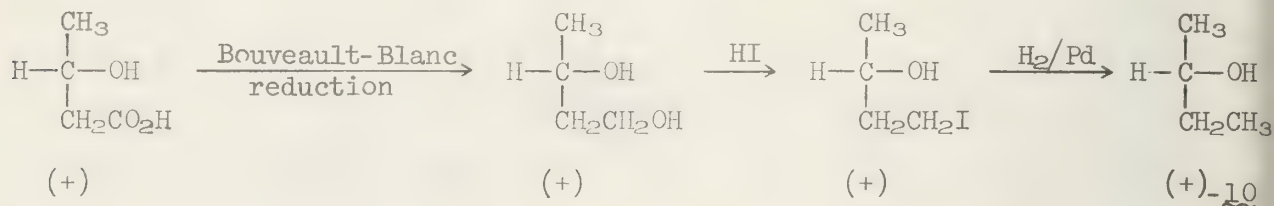


Scheme IV



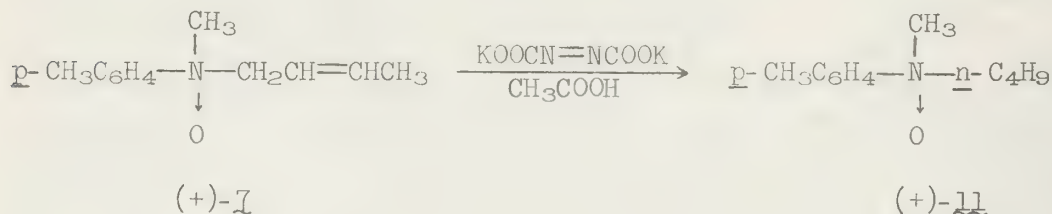
(+)-8 over platinum oxide yielded (+)-O-sec-butyl-N-methyl-p-tolylhydroxylamine [9, $[\alpha]_D + 2.38^\circ$ (c 1.52, chloroform)]. Hydrogenolysis of (+)-9 over palladium on charcoal yielded (+)-2-butanol [10, $[\alpha]_D + 1.71^\circ$ (c 1.46, EtOH)], together with N-methyl-p-toluidine. The S configuration of (+)-10 has been established (Scheme V)³³ and the same configuration is thus assigned to (+)-8 and (+)-9. Their optical purity was 14% based on the maximum rotation, $+13^\circ$,³³⁻³⁷ of the end product 10.¹⁴

Scheme V



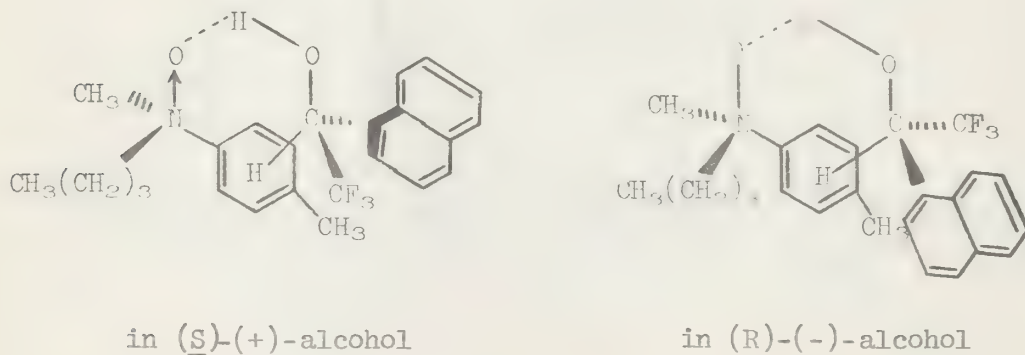
The starting amine oxide's purity and the nitrogen atom's chirality were determined by employing the Pirkle method³⁹ of magnetic nonequivalence of chemical shifts in the ^1H NMR spectrum. Compound (+)-7 was reduced by potassium azodicarboxylate (Scheme VI) to (+)-11, $[\alpha]_D + 1.65^\circ$ (c 6.50, chloroform), to simplify the correlations based on the chiral solute-chiral solvent interaction.¹⁴

Scheme VI



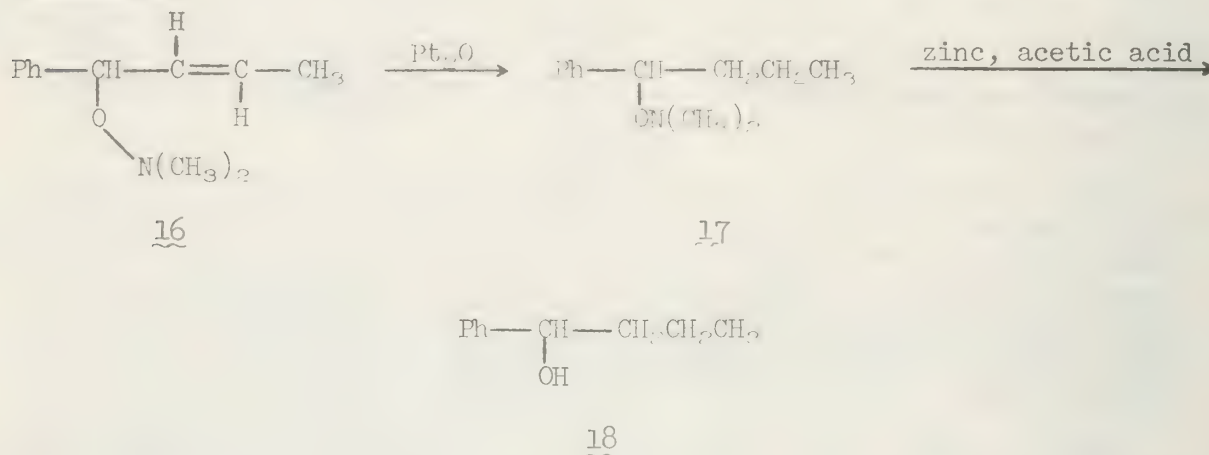
Pirkle's model employs the use of (S)-(+)- or (R)-(-)-2,2,2-trifluoro-1-(α -naphthyl)ethanol. The conformations of the solvates between (R)-(+)-N-oxide and the optically active alcohols are shown in Figure 1.

Figure 1



The trans geometry of the double bond in 16 was established by ir and ^1H NMR spectra in comparison with 1-1-phenyl-trans-2-buten-1-ol. The rearrangement product 16 was not stable enough to permit one to observe constant rotation at room temperature, so it was at once hydrogenated over platinum oxide to give (-)-O-(1-phenyl-1-ethyl)-N,N-dimethylhydroxyalanine, (-)-17, $[\alpha]_D^{26} -83.4^\circ$ (c 6.0, benzene). Reductive N-O bond fission of (-)-(17) with zinc in acetic acid afforded (-)-1-phenyl-1-butanol, (-)-18, $[\alpha]_D^{22} -31.6^\circ$ (c 10.0, benzene). See Scheme VIII. Since the S configuration of the end

Scheme VIII



product (-)-18 has been unambiguously established,⁴¹ the same configuration can be assigned to the precursors (-)-17 and 16. Consequently, the S configuration of the rearrangement product 16 was newly created at the expense of the S configuration of the substrate amine oxide 15.⁴¹

The optical purity of (-)-16 was 69% based on the reported maximum rotation $[\alpha]_D -45.9^\circ$ (c 10.0 benzene),^{44,45} thus indicating 85% optical activity was retained during the process. Inoue reported that ca. 16% racemization occurred when the hydroxylamine derivative of (-)-[α - ^3H]benzyl alcohol was treated with zinc dust in acetic acid. To assess the extent of racemization inherent to the method for N-O bond cleavage, (-)-1-phenyl-1-butanol having a rotation $[\alpha]_D^{19} -41.2^\circ$ (c 10.0, benzene), was subjected to exactly the same treatment and the recovered alcohol had a rotation of $[\alpha]_D^{20} -35.4^\circ$, which corresponded to ca. 86% retention of optical activity. Therefore, it can be concluded that the optical yield in the self-immolative asymmetric synthesis was nearly quantitative.⁴¹

The [2,3] sigmatropic rearrangements presented within this paper suggest that the process proceeds through a five-membered cyclic transition state. The transition state is of the Hückel type, and, since six electrons participate, the reaction is expected to be thermally allowed.¹⁴ Since all the evidence is consistent with an electron reorganization via a concerted, cyclic process, it would be anticipated that a reaction with such a highly ordered transition state would have an appreciable degree of stereospecificity. This conclusion had been generally accepted, but now the extensive studies of asymmetric induction have confirmed the conclusion.

It should also be pointed out that the concerted process is accompanied by a second pathway of higher activation energy, shown to involve a radical-pair mechanism. The mechanistic difference depends on the molecular environment and reaction conditions.¹⁴

BIBLIOGRAPHY

1. J. E. Baldwin and F. J. Urban, *Chem. Commun.*, 165 (1970).
2. U. Schöllkopf and K. Fellenberger, *Justus Liebigs Ann. Chem.*, 698, 80 (1966).
3. Y. Makisumi and S. Natzumoto, *Tetrahedron Lett.*, 6393 (1966).
4. A. Jefferson and F. Scheinmann, *Quart. Rev. Chem. Soc.*, 22, 391 (1968).
5. H. J. Hansen, B. Sutter, and H. Schmid, *Helv. Chim. Acta*, 51, 828 (1968).
6. V. Rautenstrauch, *Chem. Commun.*, 4 (1970).
7. J. E. Baldwin, J. DeBerrardis, and J. E. Patrick, *Tetrahedron Lett.*, 353 (1970).
8. R. W. Jemison and W. D. Ollis, *Chem. Commun.*, 294 (1969).
9. J. Meisenheimer, *Ber.*, 52, 1667 (1919).
10. J. Meisenheimer, H. Greeske, and A. Willmersdorf, *ibid.*, 55, 513 (1922).
11. R. F. Kleinschmidt and A. C. Cope, *J. Am. Chem. Soc.*, 66, 1929 (1944).
12. A. C. Cope and P. H. Towle, *ibid.*, 71, 3423 (1949).
13. V. Rautenstrauch, *Helv. Chim. Acta*, 56, 2492 (1973).
14. M. Moriwaki, Y. Yamamoto, J. Oda, and Y. Inouye, *J. Org. Chem.*, 41, 300 (1976).
15. W. E. Parham and S. H. Groen, *J. Org. Chem.*, 30, 728 (1965).
16. W. E. Parham and S. H. Groen, *J. Org. Chem.*, 31, 1694 (1966).
17. R. B. Bates and D. Feld, *Tetrahedron Lett.*, 417 (1968).
18. G. M. Blackburn, W. D. Ollis, J. D. Plackett, S. Smith, I. O. Sutherland, *Chem. Commun.*, 186 (1968).
19. J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *ibid.*, 537, 538 (1968).
20. J. E. Baldwin and D. P. Kelly, *ibid.*, 899 (1968).
21. J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *ibid.*, 1083 (1968).
22. R. M. Dodson and P. D. Hammen, *ibid.*, 1294 (1968).
23. J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *J. Am. Chem. Soc.*, 90, 4158 (1968).
24. G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969).
25. R. W. C. Cose, A. M. Davies, W. D. Ollis, C. Smith and I. O. Sutherland, *ibid.*, 293 (1969).
26. J. E. Baldwin and R. E. Hackler, *J. Am. Chem. Soc.*, 91, 3646 (1969).
27. B. M. Trost and R. F. Hammen, *ibid.*, 95, 962 (1973).
28. P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, 90, 4869 (1968).
29. V. Rautenstrauch, *Chem. Commun.*, 526 (1970).
30. A. W. Herriott and K. Mislow, *Tetrahedron Lett.*, 3013 (1968).
31. W. B. Farnham, A. W. Herriott, and K. Mislow, *J. Am. Chem. Soc.*, 91, 6878 (1969).
32. J. D. Brindle and M. S. Gibson, *Chem. Commun.*, 803 (1969).
33. W. D. Ollis, I. O. Sutherland, and Y. Thebtaranonte, *Chem. Commun.*, 653, 654 (1973).
34. W. D. Ollis, I. O. Sutherland, and Y. Thebtaranonte, *ibid.*, 657 (1973).
35. G. Smith and C. J. M. Stirling, *J. Chem. Soc.*, 1530 (1971).
36. P. A. Grieco, M. Meyers, and R. S. Finkelvor, *J. Org. Chem.*, 39, 119 (1974).
37. S. Braverman and H. Mechoulam, *Tetrahedron*, 30, 3883 (1974).
38. W. Klyne, "Progress in Stereochemistry," Vol. 1, Butterworths, London, 1954, p 183.
39. W. H. Pirkle, R. L. Muntz, and I. C. Paul, *J. Am. Chem. Soc.*, 93, 2817 (1971).
40. W. H. Pirkle, S. D. Beare, and T. G. Burlingame, *J. Org. Chem.*, 34, 470 (1969).

- 41. Y. Yamamoto, J. Oda, and Y. Inouye, J. Org. Chem., 41, 303 (1976).
- 42. K. Freudenberg and F. Rhino, Ber., 57, 1547 (1924).
- 43. R. MacLeod, F. S. Welch, and H. S. Mosher, J. Am. Chem. Soc., 82, 876 (1960).
- 44. J. Kenyon and S. M. Partridge, J. Chem. Soc., 128 (1936).
- 45. K. Mislow and C. L. Hamermesh, J. Am. Chem. Soc., 77, 1590 (1955).
- 46. R. K. Hill and N. W. Gillman, Chem. Commun., 619 (1967).
- 47. D. J. Cram, J. Am. Chem. Soc., 71, 3884 (1949).
- 48. D. J. Cram, J. Am. Chem. Soc., 74, 2149 (1952).

HYDROZIRCONATION

Reported by Kenneth J. Allison

April 15, 1976

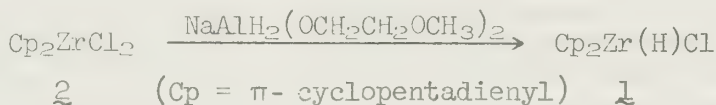
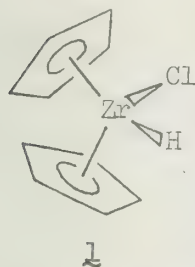
INTRODUCTION AND SCOPE

The utility of the hydrozirconation reaction in organic synthesis was first reported in 1974.¹ Since then, this process has been found to be an effective means of synthesizing, under mild conditions and in high yield, a variety of organic compound types from unsaturated hydrocarbons. Other intriguing aspects of this reaction are its stereospecificity, its regioselectivity, and its capacity for effecting remote functionalization.

This seminar will discuss the scope and mechanism of hydrozirconation reactions, and compare them with analogous reactions involving boranes, alanes, or other transition metal hydrides.

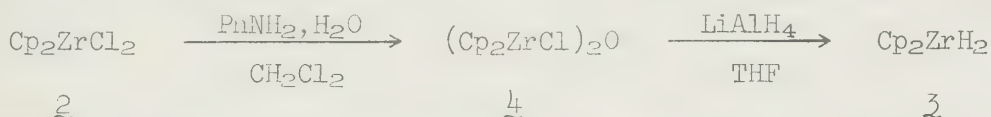
SYNTHESIS OF THE REAGENTS

The zirconium reagent used exclusively by Schwartz and coworkers¹⁻⁶ in their series of reports on hydrozirconation has been bis(π -cyclopentadienyl)-zirconium hydrido chloride, (1) which they prepared by slowly adding Vitride (0.5 mol.) to a solution of the corresponding dichloride (2) in tetrahydrofuran. Compound (1), which is isolated as a white precipitate, reacts with



moisture and is slightly light sensitive. Wailes and coworkers^{7,8} first synthesized 1 in 90% yield in a similar manner using one hydride equivalent of lithium aluminum hydride or lithium tri-*t*-butoxyaluminum hydride. They also prepared the dihydride (3) in 66% yield from

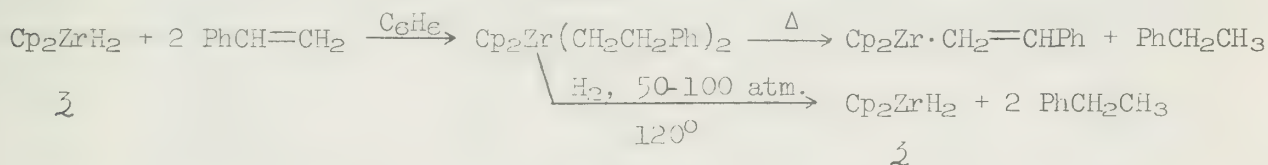
the reaction of the oxygen bridged compound (4) with lithium aluminum hydride. Compound 4 was prepared⁹ by the action of aniline and water on commercially



available¹⁰ 2 in methylene chloride. The insolubility and lack of volatility of the compounds indicate that the hydrides 1 and 3 are polymeric, while infrared spectral studies¹¹ indicate the presence of bridging hydrido groups.

HYDROZIRCONATION OF ALKENES

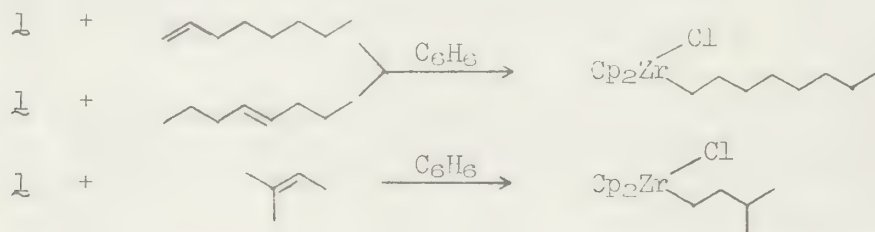
The first reactions of the zirconium(IV) hydrides 1 and 3 with olefins were reported by Wailes and coworkers.¹² The dihydride reacted with olefins in boiling benzene to form unstable, soluble intermediate dialkylzirconium(IV) complexes, which decomposed to yield a dark solid identified as zirconocene, together with equal amounts of alkanes and alkenes (the latter complexed with zirconocene) (eq. 3). When the reaction of olefins with 3 was run under



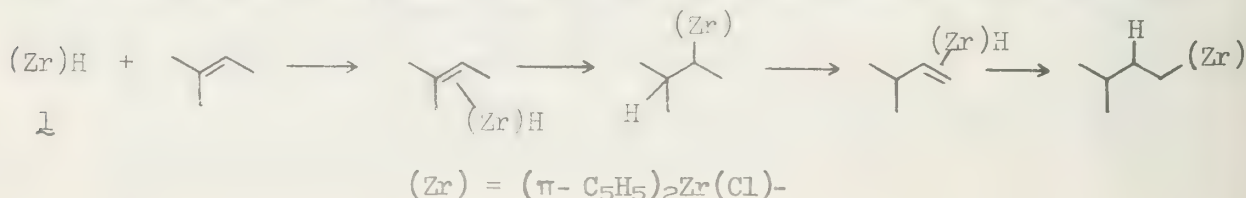
hydrogen (50-100 atm.), catalytic hydrogenation took place to form the alkanes in quantitative yield, regenerating the dihydride 3. The thermal instability

of the dialkylzirconium derivatives with respect to β -elimination of hydrogen explains why only the dimethyl and dibenzyl derivatives, which contain no β -hydrogens, have been isolated.

The monohydride **1** formed more stable monoalkyl derivatives with cyclohexene, 4-vinylphenyl, and 2-methyl-2-butene, but the points of attachment of the zirconium atoms to the alkyl groups were not established with certainty.¹² Due to the increased stability of the monoalkyl derivatives, catalytic hydrogenation required longer reaction times and/or higher temperatures than for the dialkylzirconium(IV) derivatives. Schwartz and co-workers¹ formed monoalkylzirconium(IV) complexes from the reaction of **1** with olefins. Yields in excess of 90% were obtained and the products were characterized by ¹H NMR. The alkylzirconium(IV) complexes are moisture sensitive, but are not readily decomposed by dry air. They are prepared under an argon atmosphere from monosubstituted and disubstituted olefins by shaking a suspension of a slight excess of **1** with the olefin in benzene for a few hours at room temperature. Relative rates of addition for the olefins studied were: 1-octene > *cis*-4-octene > *trans*-4-octene > methylenecyclohexane > cyclopentene > cyclohexene >> 2-methyl-2-butene. This order of reactivity may reflect the relative ease of fitting the olefins into the sterically crowded bent "sandwich" structure of **1**. Hydrozirconation of hindered olefins can be facilitated by elevating the temperature to 40°, while 1-methylcyclohexene, cyclooctene, and tetramethylethylene fail to react even at this temperature overnight. The position of attachment of the zirconium atom to the alkyl group is the least sterically hindered, accessible position of the molecule as a whole, resulting from migration of the zirconium atom from the point of initial attachment. The exception is that the migration has not been observed to occur past a tertiary carbon at room temperature. That is, if the starting olefin contained a double bond anywhere within a straight chain alkyl group, the zirconium atom would ultimately be attached to the primary end of that chain. For the hydrozirconation of 4-octene, the zirconium migration takes place so fast that when the reaction is monitored by ¹H NMR spectroscopy, only the starting olefin and the ultimate 1-alkylzirconium(IV) derivative are detected, suggesting that the isomerization rate is at least as fast as the rate of olefin insertion into the Zr-H bond.



Initial olefin insertion probably occurs by a two-step mechanism analogous to that proposed for other transition metal hydride additions to olefins.¹³⁻¹⁵ The olefin, acting as a Lewis base, coordinates to the one remaining vacant hybrid orbital on the metal,⁸ then rapidly inserts into the Zr-H bond. The isomerization to place the zirconium on the least sterically hindered position attainable is postulated to involve a series of rapid β -hydride eliminations and reallitions. This mechanism, resulting in a net 1,2-hydride shift,¹⁶ has been shown to occur in the reaction of deuterated



Acetylene	Product Ratio A:B (refer to eq. 1)		
	Initially Observed	After treatment with 1	Dicyclohexylborane analog ²⁵
R=H; R'= <u>n</u> -C ₄ H ₉ -	>98:<2	--	--
R=CH ₃ ; R'=CH ₃ CH ₂ -	55:45	89:11	--
R=CH ₃ ; R'=CH ₃ CH ₂ CH ₂ -	69:31	91:9	67:33
R=CH ₃ ; R'=(CH ₃) ₂ CHCH ₂ -	55:45	>95:<5	--
R=CH ₃ ; R'=(CH ₃) ₂ CH-	84:16	>98:<2	92:8
R=CH ₃ ; R'=(CH ₃) ₃ C-	>98:<2	--	>97:<3

Allylic rearrangement products²⁴ were not observed and the regioselectivity was found to be generally greater than that observed for hydroboration with hindered boranes.²⁵

REACTIONS OF ALKYLZIRCONIUM(IV) COMPLEXES WITH ELECTROPHILES

Schwartz and coworkers¹ treated the alkylzirconium(IV) complexes derived from olefins with a range of electrophiles to give the products and yields (based on the alkylzirconium(IV) species) shown in Table II. Protonolysis

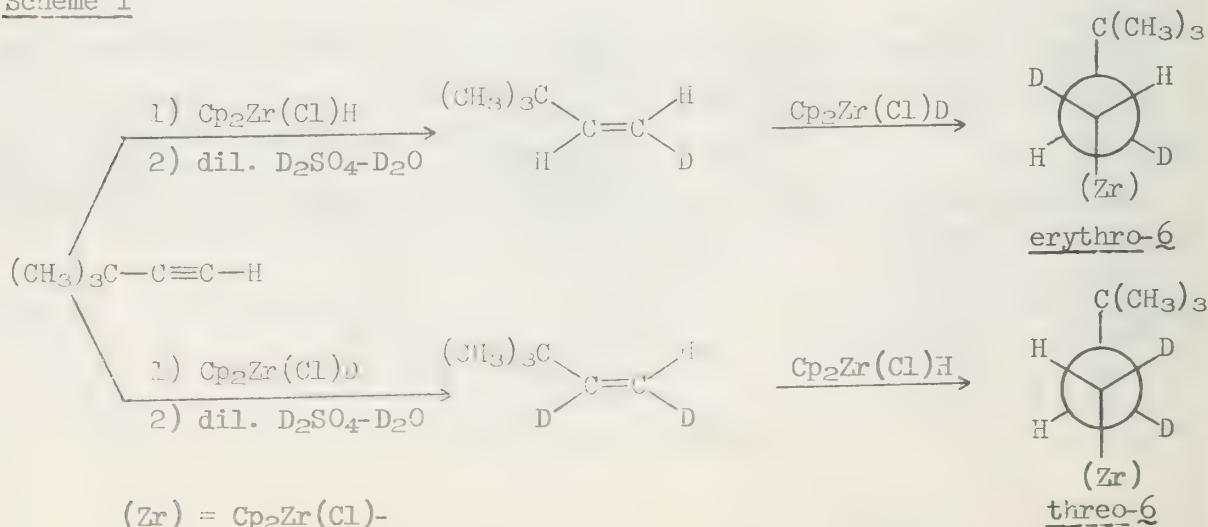
Table II. Products from Reactions of Electrophiles with Alkylzirconium(IV) Complexes Derived from Olefins.

Olefin	Electrophile	Product	Yield (%)
1-Octene or 4-octene	H ⁺	Octane	100
	Br ₂	1-Bromooctane	96
	I ₂	1-Iodooctane	91
	PhICl ₂	1-Chlorooctane	65
	CH ₃ COCl	2-Decanone	80
2-Methyl-2-butene	Br ₂	1-Bromo-3-methylbutane	100
	CH ₃ COCl	5-Methyl-2-hexanone	72
Cyclohexene	Br ₂	Bromocyclohexane	95

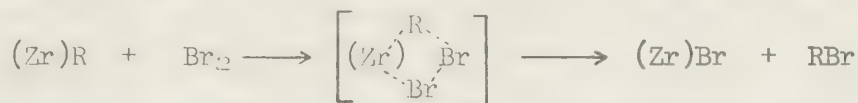
in dilute hydrochloric acid took place instantly at 0° to yield the alkane. Halogenation also occurred rapidly upon addition of bromine at 0° or iodobenzene dichloride at room temperature to a benzene solution of the alkylzirconium(IV) complex, as did iodination upon adding the alkylzirconium solution to iodine in carbon tetrachloride at room temperature. Acetyl chloride in benzene reacted more slowly with the alkylzirconium complexes at room temperature to yield ketones. In each case, except protonolysis, a bis(π-cyclopentadienyl)zirconium dihalide can be recovered and recycled to 1.

The mechanism of the electrophilic cleavage of the carbon-zirconium bond was also studied by Schwartz and coworkers,⁵ who prepared erythro and threo-alkylzirconium(IV) complexes by the hydrozirconation of t-butylacetylene (Scheme I). Upon treatment of a benzene solution of 6 with an equivalent amount of bromine at 10°, the resulting allyl bromide was isolated and found by ¹H NMR²⁶ to be the product resulting from retention of configuration. The reaction of 6 with *N*-bromosuccinimide (NBS) or iodine also demonstrated retention of configuration.

Scheme I



For zirconium(IV) complexes, however, the d^0 electronic configuration of the metal makes oxidative addition extremely unlikely. A closed transition state (four-center or S_E1)²⁹ involving attack by the halogen molecule, such as



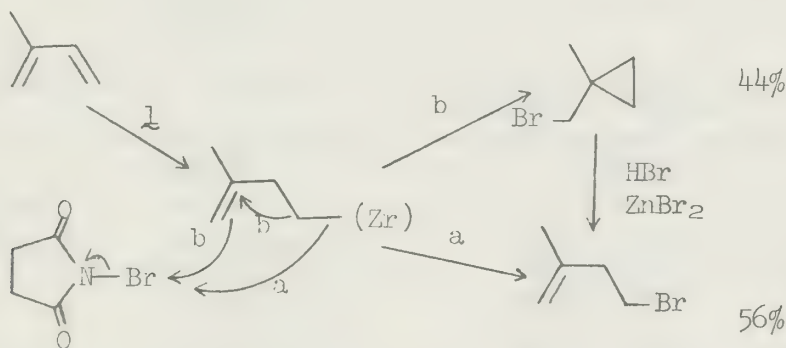
that proposed for organomercurials,³⁰ is suggested, but an S_E2 (open) mechanism involving attack by the free electrophile on the carbon-metal bond cannot be ruled out. The S_E1 mechanism could probably be extended to include the reactions of alkylzirconium(IV) complexes with other electrophiles as well as catalytic hydrogenation of the complexes.

The addition of **1** to 1,3-dienes⁶ was found to occur via 1,2-addition to give γ, δ -unsaturated (homoallylic) zirconium(IV) complexes in 80-90% yield. The reaction of **1** with 1,3-dienes occurred at a rate about 50 times slower than the reaction of **1** with terminal olefins. No products resulting from dimetalation or double bond migration were observed.

Sterically hindered boranes¹⁹ such as bis(3-methyl-2-butyl)borane (disiamylborane) have been found to undergo 1,2-addition to the 1,3-dienes myrcene^{31a} and 1,3-pentadiene^{31b} to give, when followed by oxidation, the corresponding γ, δ -unsaturated alcohols in 60% and 74% yields, respectively. Aluminum hydrides³² and other boron hydrides¹⁹ generally doubly metalate 1,3-dienes or give mixtures of products, while most transition metal hydrides³³ yield allylic complexes.

γ, δ -Unsaturated bromides were prepared by the reaction of the corresponding zirconium complex with NBS in benzene. However, 3-alkyl substituted complexes yielded isomeric cyclopropylcarbinyl bromides as 25-44% of the halogenated product by the mechanism shown in Scheme II. These cyclic products

Scheme II



were easily converted to γ, δ -unsaturated bromides by reaction with zinc bromide in hydrobromic acid.³⁴ In each case studied, the total yield of bromide was about 85%.

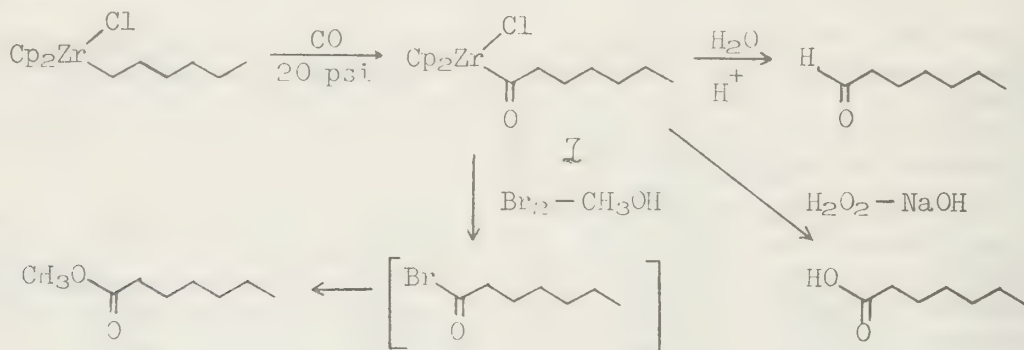
Treatment of the alkenylzirconium(IV) complexes obtained from alkynes³ with N-bromosuccinimide, N-chlorosuccinimide, or iodine rapidly produced the corresponding vinylic halides in 55-100% yield with retention of stereochemistry and positional isomerism. Through the use of lithium dialkylcuprates,³⁵ the vinylic halides obtained from dialkylacetylenes can then be converted to trialkylolefins.

REACTIONS OF ALKYLZIRCONIUM(IV) COMPLEXES WITH CARBON MONOXIDE

Schwartz and coworkers² have found that carbon monoxide undergoes insertion, cleanly and in high yield, into the C-Zr bond of alkylzirconium(IV) complexes prepared by the reaction of **1** with olefins. Since no zirconium

carbonyl species was detected at any point in the reaction, a proposed sequence for the "insertion" mechanism involves rapid, reversible coordination of carbon monoxide to the vacant metal hybrid orbital followed by slow migration of the alkyl group to the coordinated carbon monoxide.^{14, 36} The insertion reaction takes place upon stirring a benzene solution of the alkylzirconium(IV) complex for several hours under 20 psi of carbon monoxide, with cycloalkyl complexes undergoing insertion faster than *n*-alkyl complexes; similar relative rates are found for Fe-C carbonyl insertion.³⁷ The resulting acylzirconium(IV) complexes (**1**) can be converted into the corresponding aldehydes, carboxylic acids, or esters as shown in Scheme III.

Scheme III



Addition of dilute hydrochloric acid to a benzene solution of **1** immediately yields the aldehyde. Treatment of **1** with aqueous sodium hydroxide followed by 50% hydrogen peroxide gives the carboxylic acid upon acidification. Slow addition of bromine in methanol to a benzene solution of **1** at room temperature yields the ester by way of an acyl bromide intermediate. Representative yields of derivatives, based on the alkylzirconium complex, are shown in Table III. Improved yields of acid or ester were attained by treatment of **1** with NBS followed by water or alcohol.

Table III. Products from Carbonylation of Alkylzirconium(IV) Complexes Derived from Olefins.

Olefin	Work-up	Product	Yield (%)
1-Hexene or 3-hexene	dil. HCl	Heptanal	99
	Br ₂ - CH ₃ OH	Methyl heptanoate	51
	NaOH - H ₂ O ₂	Heptanoic acid	77
2-Methyl-2- butene	dil. HCl	4-Methylpentanal	71
	Br ₂ - CH ₃ OH	Methyl 4-methylpentanoate	50
	NaOH - H ₂ O ₂	4-Methylpentanoic acid	26
Cyclohexene	dil. HCl	Cyclohexanecarboxaldehyde	97
	Br ₂ - CH ₃ OH	Methyl cyclohexanecarboxylate	57

As in the case of alkylzirconium(IV) complexes, the cleavage of the Zr-C bond in acylzirconium(IV) complexes cannot occur via an oxidative addition mechanism such as that proposed for transition metal-carbon bonds in other protonolysis,³⁸ carboxylation,³⁹ or halogenation²⁸ reactions. Direct electrophilic attack on the acyl carbon atom of the complexes by hydrogen peroxide or bromine was proposed as the mechanism of cleavage.

γ, δ -Unsaturated aldehydes⁶ were also prepared in high yield from 1,3-dienes by carbonylation and hydrolysis of γ, δ -unsaturated alkylzirconium(IV) complexes, which added carbon monoxide faster than their saturated analogues.

OXIDATIONS OF ALKYLZIRCONIUM(IV) COMPLEXES TO ALCOHOLS

Alkylzirconium(IV) complexes can be oxidized under mild conditions by a variety of oxidizing agents to form alcohols in high yield.⁴ Coupled with hydrozirconation, this method leads exclusively to the formation of terminal alcohols on an unbranched carbon chain containing either a terminal or an internal double bond.

Protic oxidizing agents ($\text{H}_2\text{O}_2/\text{NaOH}$, $t\text{-C}_4\text{H}_9\text{OOH}$, and $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$) lead directly to the alcohols, with some alkane by-products resulting from protonolysis. The reaction takes place within minutes upon addition of an excess of the oxidizing agent to a benzene solution of the alkylzirconium complex. The alcohols were recovered by reduced pressure distillation, in moderate yields based on the alkylzirconium(IV) complex (Table IV).

Dry oxygen functions as a slower, less expensive oxidizing agent which, when followed by hydrolysis, often gave higher yields of the alcohol than the protic agents. The reactions are clean and involve stirring a solution of the alkylzirconium(IV) complex under an atmosphere of dry oxygen for several hours, followed by hydrolysis of the alkoxyzirconium(IV) complex with dilute hydrochloric acid to give the corresponding alcohol. Moderate yields were obtained based on the alkylzirconium(IV) complex (see Table IV). The presence of an alkoxyzirconium(IV) intermediate was demonstrated by spectral comparison to those previously reported.⁴⁰ The progress of the oxidation could be followed

Table IV. Products from Oxidation of Alkylzirconium(IV) Complexes Derived from Olefins.

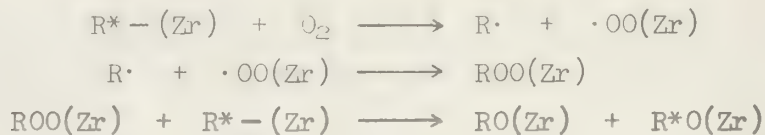
Olefin	Oxidizing agent	Product	Yield (%)
1-Octene or <u>cis</u> -4-octene	$\text{H}_2\text{O}_2/\text{NaOH}(\text{aq})$	1-Octanol	69
	$t\text{-C}_4\text{H}_9\text{OOH}$		72
	$m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$		45
	O_2 ; H_3O^+		57
3,3-Dimethyl-1-butene	$t\text{-C}_4\text{H}_9\text{OOH}$	3,3-Dimethyl-1-butanol	59
Cyclohexene	$\text{H}_2\text{O}_2/\text{NaOH}(\text{aq})$	Cyclohexanol	29
	$t\text{-C}_4\text{H}_9\text{OOH}$		40
	O_2 ; H_3O^+		76
2-Methyl-2-butene	O_2 ; H_3O^+	3-Methyl-1-butanol	70
1,5-Hexadiene	O_2 ; H_3O^+	5-Hexen-1-ol	80
Isoprene	O_2 ; H_3O^+	3-Methyl-3-buten-1-ol	77

by measuring oxygen uptake. The yields obtained were generally inferior to those obtained via hydroboration-oxidation,¹⁸ although the facile isomerization of internal olefins to give terminal alcohols was an attractive feature.

Schwartz and coworkers,⁴ noting the interest^{41,42} in the mechanism of autoxidation of metal alkyls by oxygen and the scarcity of mechanistic information for the autoxidation of transition metal alkyls, undertook a study of the mechanism of oxidation by oxygen of alkylzirconium(IV) complexes. They found the following: (i) Each mole of alkylzirconium(IV) complex took up 0.5 mole of oxygen; (ii) The only significant product found after the oxidation was the alkoxide; (iii) Oxidation of the chiral complex 6 by oxygen proceeded with approximately 50% retention and 50% racemization of configuration, whereas oxidation by protic agents gave only retention, indicating electrophilic attack;

(iv) The *t*-butylperoxyzirconium complex reacted rapidly with the chiral complex 6 to yield equal amounts of the *t*-butyl and chiral alkoxyzirconium(IV) complexes, with complete retention of configuration of the chiral derivative. Based on these results, Schwartz proposed the mechanism shown in Scheme IV for the oxidation of alkylzirconium(IV) complexes by oxygen.

Scheme IV



R^* = chiral alkyl

R = racemic alkyl

$(Zr) = Cp_2Zr(Cl)-$

Attack by oxygen induces homolysis of the C-Zr bond of the alkylzirconium complex, with the resulting racemized alkyl radical being trapped by $Cp_2Zr(Cl)OO\cdot$ to form the racemic alkylperoxy complex, which reacts rapidly with another molecule of the chiral alkyl complex, this time with retention of configuration, to form two molecules of the alkoxide, with the observed result of 50% retention and 50% racemization. The formation of 3% cyclopentylmethanol in the autoxidation and hydrolysis of the 5-hexenylzirconium(IV) complex also supports the formation of alkyl radical intermediates, since the 5-hexenyl radical has been found to rearrange to the cyclopentylmethyl radical.^{42a} Analogous schemes have been proposed for the autoxidation of Grignard^{42a} and lithium^{42b} reagents. Complete racemization has been shown to occur in the reaction of alkylcobalt complexes with oxygen to give alkylperoxycobalt complexes.⁴³

CONCLUSIONS

Hydrozirconation is a relatively new reaction which proceeds under mild conditions with high regioselectivity and good yields and appears to be the method of choice for a number of organic transformations, including (i) functionalization at the terminal position of *n*-alkyl chains containing an internal double bond, (ii) regioselective synthesis of trialkylolefins and *cis*-dialkyl substituted vinylic halides from disubstituted acetylenes, and (iii) functionalization at only one position in 1,3-dienes. Much more work needs to be done toward understanding the mechanism of hydrozirconation reactions, as well as extending the scope and demonstrating the utility of the reaction in routine organic synthesis.

REFERENCES

1. D. W. Hart and J. Schwartz, *J. Am. Chem. Soc.*, 96, 8115 (1974).
2. C. A. Bertelo and J. Schwartz, *ibid.*, 97, 228 (1975).
3. D. W. Hart, T. F. Blackburn, and J. Schwartz, *ibid.*, 97, 679 (1975).
4. T. F. Blackburn, J. A. Labinger, and J. Schwartz, *Tetrahedron Lett.*, 3041 (1975).
5. J. A. Labinger, D. W. Hart, W. E. Seibert III, and J. Schwartz, *J. Am. Chem. Soc.*, 97, 3851 (1975).
6. C. A. Bertelo and J. Schwartz, *ibid.*, 98, 262 (1976).
7. P. C. Wailes and H. Weigold, *J. Organometal. Chem.*, 24, 405 (1970).
8. P. C. Wailes, R. S. P. Coutts, and H. Weigold, "Organometallic Chemistry of Titanium, Zirconium, and Hafnium," Academic Press, New York, N.Y., 1974, pp 1-6, 116-155.
9. A. F. Reid, J. S. Shannon, J. M. Swan and P. C. Wailes, *Aust. J. Chem.*, 18, 173 (1965).
10. Ventron Corp. - Alfa Products.

11. L. Banford and G. E. Coates, *J. Chem. Soc., A*, 1008 (1969).
12. P. C. Wailes, H. Weigold, and A. P. Bell, *J. Organometal. Chem.*, 43, C32 (1972).
13. C. P. Casey and C. R. Cyr, *J. Am. Chem. Soc.*, 95, 2240 (1973).
14. C. A. Tolman, *Chem. Soc. Rev.*, 1, 337 (1972).
15. (a) J. Chatt and B. L. Shaw, *J. Chem. Soc.*, 5075 (1962); (b) J. Chatt, R. S. Coffey, A. Gough, and D. T. Thompson, *J. Chem. Soc., A*, 190 (1968).
16. M. Orchin and W. Rupilius, *Catal. Rev.*, 6, 85 (1972).
17. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 89, 561 (1967).
18. H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972, Chapters XV, XVI, and XVII.
19. H. C. Brown, "Organic Syntheses via Boranes," Wiley, New York, N.Y., 1975.
20. L. I. Zakharkin and O. Y. Okhlobystin, *Bull. Acad. Sci. USSR*, 1236 (1958).
21. M. A. Bennet and R. Charles, *J. Am. Chem. Soc.*, 94, 666 (1972).
22. (a) R. A. Schunn, *Inorg. Chem.*, 9, 2567 (1970); (b) C. A. Tolman, *J. Am. Chem. Soc.*, 94, 2994 (1972); (c) R. Cramer and R. V. Lindsey Jr., *ibid.*, 88, 3534 (1966).
23. P. C. Wailes, H. Weigold, and A. P. Bell, *J. Organometal. Chem.*, 27, 373 (1971).
24. J. Schwartz, D. W. Hart, and B. S. McGiffert, *J. Am. Chem. Soc.*, 96, 5613 (1974).
25. G. Zweifel, G. M. Clark, and N. L. Polston, *ibid.*, 93, 3395 (1971).
26. P. L. Bock, D. J. Boschetto, J. R. Rasmussen, J. P. Demers, and G. M. Whitesides, *ibid.*, 96, 2814 (1974).
27. T. C. Flood and F. J. DiSanti, *Chem. Commun.*, 18 (1975).
28. (a) F. R. Jensen, V. Madan, and D. H. Buchanan, *J. Am. Chem. Soc.*, 93, 5283 (1971); (b) S. N. Anderson, D. H. Ballard, J. Z. Chrzastowski, D. Dodd, and M. D. Johnson, *Chem. Commun.*, 685 (1972).
29. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N.Y., 1968, pp 442-446.
30. F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N.Y., 1968, pp 39-43, 92-97.
31. (a) H. C. Brown, K. P. Singh, and B. J. Garner, *J. Organometal. Chem.*, 1, 2 (1963); (b) G. Zweifel, K. Nagase, and H. C. Brown, *J. Am. Chem. Soc.*, 84, 190 (1962).
32. L. I. Zakgarkin and L. A. Savina, *Izv. Akad. Nauk SSSR, Ser. Khim., Engl. Ed.*, 72 (1967).
33. (a) C. K. Brown, W. Mowat, G. Yagupsky, and G. Wilkinson, *J. Chem. Soc., A*, 850 (1971); (b) M. S. Wrighton and M. A. Schroeder, *J. Am. Chem. Soc.*, 96, 6235 (1974).
34. (a) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, 90, 2882 (1968); (b) J. D. Roberts and R. H. Mazur, *ibid.*, 73, 2509 (1951).
35. (a) E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, 90, 5615 (1968); (b) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *ibid.*, 89, 4245 (1967).
36. (a) A. Wojcicki, *Advan. Organometal. Chem.*, 11, 88 (1973); (b) J. Tsuji, *Acc. Chem. Res.*, 2, 144 (1968); (c) D. Medema, R. van Helden, and C. F. Kohll, *Inorg. Chim. Acta*, 3, 255 (1969).
37. M. Green and D. J. Westlake, *J. Chem. Soc., A*, 367 (1971).
38. U. Belluco, G. Deganello, R. Pietropaolo, and P. Uguagliati, *Inorg. Chim. Acta Rev.*, 4, 7 (1970).
39. K. M. Nicholas and M. Rosenblum, *J. Am. Chem. Soc.*, 95, 4449 (1973).
40. D. R. Gray and C. H. Brubaker, *Inorg. Chem.*, 10, 2143 (1971).
41. T. G. Brilkina and V. A. Shushunov, "Reactions of Organometallic Compounds with Oxygen and Peroxides," Iliffe, London, 1969.
42. (a) C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, 92, 6609 (1970); (b) E. J. Panek and G. M. Whitesides, *J. Am. Chem. Soc.*, 94, 8768 (1972).
43. F. R. Jensen and R. C. Kiskis, *J. Organometal. Chem.*, 49, C46 (1973).

APPLICATION OF THE SATURATION METHOD TO INTRAMOLECULAR HYDROGEN BONDING IN CYCLIC PEPTIDES.

Reported by Jim Hauske

April 26, 1976

Introduction

Conformational preferences of biologically active peptides in solution continues to be an area of active research.^{1,2} Present research on peptide conformations largely concerns determination of intramolecular hydrogen bonding for amide (N-H) protons. Unquestionably, nuclear magnetic resonance (NMR) spectroscopy has produced a plethora of information in the area of solution conformation. Only recently, however, was an NMR method developed which elucidated definitively intramolecularly hydrogen bonded conformations for peptides, especially cyclic peptides. This method, known as the saturation method, has now been employed to finalize solution conformations for a number of peptides, including the linear peptide angiotensin II,²⁶ and the cyclic peptides gramicidin S,²⁷ oxytocin¹¹ and lysine-vasopressin.¹⁶ Previously, NMR conformational analysis of peptides in solution involved determination of the extent of solvent exposure of specific NH hydrogens. The methods utilized consisted of: (1) rates of NH proton exchange with labile solvent hydrogens;^{3,4} (2) temperature dependence of chemical shifts of amide proton (NH) resonances;^{5,6} (3) chemical shift dependence of amide proton (NH) with solvent variation;^{7,8} and (4) degree of resonance broadening with the addition of a paramagnetic substance.^{9,10} Generally, these methods yielded only partial analysis, proving either troublesome or inaccurate.

This seminar will illustrate the usefulness of the saturation method in unraveling conformational problems presented by cyclic peptides with 6-12 amino acid residues. First, we shall review existing methods.

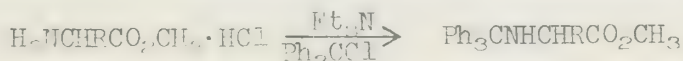
I. CHEMICAL SHIFT AND COUPLING CONSTANT DETERMINATIONS

Generally, only moderate changes in proton resonances of free amino acids follow their incorporation into a polypeptide; therefore, NMR data for monomers are often used to make assignments in the spectra of polypeptides. The notion that perturbations in chemical shift are small going from monomers of amino acids to polypeptides stems from excellent correlation of calculated and observed spectral parameters.¹⁷ One of the drawbacks of this "working" hypothesis is that resonances having similar chemical shifts in differing monomers are relatively unchanged once incorporated into a peptide. This results in an overlapping of signals and is a rather vexing problem. To overcome this difficulty two procedures are utilized: (1) decoupling; and (2) functionalization.

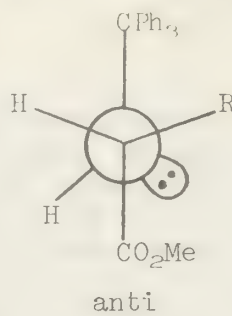
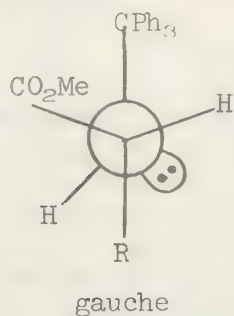
For example,¹⁸ in the case of a dipeptide (which exists as a zwitterion at neutral pH), addition of base to a neutral solution shifts the protons of R to higher field; while addition of acid will shift the protons of R' to lower field. The dipeptides glycylalanine (Gly-Ala) and alanylglycine (Ala-Gly) illustrate the method. In Gly-Ala the glycyl CH₂ singlet undergoes an upfield shift (-0.55 ppm) after base addition and the alanyl CH a downfield shift after acid addition (+0.23 ppm).

In Ala-Gly, on the other hand, the NMR behavior is reversed.

Another example of functionalization is illustrated by N-tritylation.¹⁹

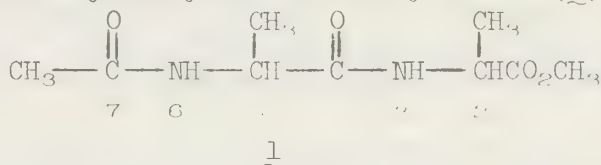


In methyl esters of α -amino acids, the carbomethoxy peak is found upfield by 0.2-0.9 ppm after N-tritylation. The chemical shift differences were interpreted in terms of preferred conformations. The ester methyl protons will be most influenced by the trityl function in the gauche conformation,



and least influenced in the anti form. As R becomes bulkier, the gauche conformation is more heavily populated, shifting the CO_2CH_3 resonance upfield. One would predict a small effect for glycine, where $\text{R}=\text{H}$, and a larger effect for valine, where $\text{R}=\text{CH}(\text{CH}_3)_2$. Experimentally $\Delta\delta$'s of 0.27 and 0.78 ppm respectively, are observed.

Evidence for preferred rotational states may be obtained from a consideration of chemical shift and coupling constant information. Consider the example of N-acetylalanylalanine methyl ester (1).²⁰ Conformations



of this peptide are inferred from an examination of the vicinal coupling constant for N(6)H-C(5)H. The value of this coupling is then related to the dihedral angle; thus, to initiate such an examination it is necessary to differentiate N(3)H and N(6)H signals.

The analysis is accomplished by identifying the 2- and 5-methyl resonances, which form overlapping doublets (81.4) in deuterium oxide. The resonance occurring at higher field is unchanged when the ester group is partially hydrolyzed (by addition of sodium deuterio oxide), whereas the lower field doublet is reduced in intensity and a new doublet appears at higher field than in the original group. The low field doublet must then be due to the 2- CH_3 , because only this group will be influenced (shielded) by the change $\text{CO}_2\text{CH}_3 \rightarrow \text{CO}_2^-$.

Decoupling experiments allow assignment of the remaining resonances. Irradiation at the H-2 methine frequency (84.25) simultaneously decouples the 2- CH_3 and N(3)H doublets, while irradiation at the C-5 methine frequency (84.7) decouples the C-5 methyl and N(6)H. Once one establishes which resonance corresponds to a particular amino acid residue, coupling constants are easily measured. The vicinal coupling constants of N(6)H-C(5)H are in the range 7.3 Hz to 7.8 Hz (Table 1). These values, on the basis of a coupling constant-dihedral angle relationship²¹ ($\phi = 0$, $J \sim 8\text{Hz}$), suggest a marked preference for eclipsed rotamers (Fig. 1).

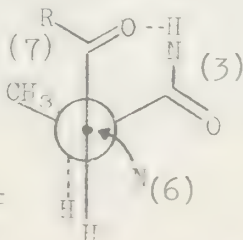


Figure 1

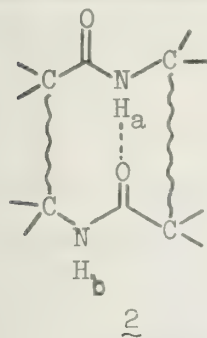
Projection along N(6)-C(5) bond.

Table 1. Observed spin-spin coupling constants $N(6)H-C(4)H$ protons and chemical shifts of $N(6)H$ proton.

solvent		J cis	δ ppm
$CDCl_3 + CCl_4$	(1:9)	7.6	6.60
	(1:5)	7.7	6.87
	(1:3)	7.8	7.04

II. EXCHANGE RATES.

In attempts to determine solution conformations of peptides, exchange data were utilized to distinguish amide ($N-H$) protons which were intramolecularly hydrogen bonded from those which were not.^{8,12,13,31} Consider the hypothetical solution conformation of polypeptide 2. Note the two different amide ($N-H$) protons labelled a and b. Assuming the conformation illustrated, one might expect that exchangeable proton, H_b , would have a faster rate of exchange than H_a . Presumably, differences in exchange would reflect the facts that, H_a is sequestered from solvent and H_a is also "bound" to the carbonyl oxygen.



During the total conformational analysis of gramicidin S^{14} exchange data were accumulated (Table 2). Note that in tetradeuterio methanol ornithine amide protons and phenylalanine amide protons have half-lives considerably shorter than similar protons of valine and leucine (hours vs. weeks). These data reflect intramolecular hydrogen bonds for valine and leucine. However, this work failed to recognize the ability of side chains on amino acids to catalyze exchange reactions;^{3,5,6} thus, the experiment yielded only tentative hydrogen bonding information.

Table 2. Half-lives for $N-H$ protons.

Solvent	valine		ornithine		leucine		phenylalanine	
	ppm ^a	t/2 ^b	ppm	t/2	ppm	t/2	ppm	t/2
CD_3OD	7.7	2 wk.	8.7	24 hr.	8.8	1 wk.	8.9	0.5 hr.
$DMSO-d_6$								
+5%	7.2	2 wk.	8.7	0.5 hr.	8.35	1 wk.	9.15	0.5 hr.
D_2O								

(a) ppm measured from internal TMS. (b) half-life.

So although exchange data are easily obtained and easily interpretable, factors which often perturb rates of exchange may lead to untenable conclusions based on the experimental results.

III. TEMPERATURE EFFECTS.

An example of information obtained from temperature variation is found in the case of the cyclic hexapeptide Pro-Ser-Gly-Pro-Ser-Gly.¹⁵ In both water and dimethylsulfoxide- d_6 temperature dependence of chemical shifts for peptide ($N-H$) protons yielded information concerning intramolecular hydrogen bond participation. Upfield shifts of resonances for protons capable of forming hydrogen bonds are attributed to the breaking of an increasing fraction of such bonds with increasing temperature. Obviously, this dependence should be small for intramolecular hydrogen bonds but substantial for those capable of forming only external hydrogen bonds to solvent. Figure 2 shows

the result of chemical shift variation with increasing temperature for serine and glycine NH absorptions.

Thus far, the utility of temperature variation is convincing. Unfortunately, there are many cases which are clearly ambiguous. For example, the amide (N-H) protons of lysine-vasopressin, a cyclic nonapeptide, have anomalous temperature dependence.¹⁰ Coupling constant and exchange data point toward intramolecular hydrogen bonding; yet the temperature coefficients are non-zero. Figure 2 illustrates the temperature dependence.

Figure 2: Chemical shift variation of hexapeptide N-H protons.

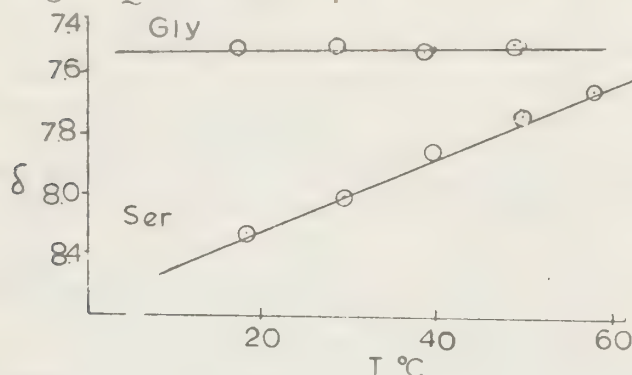
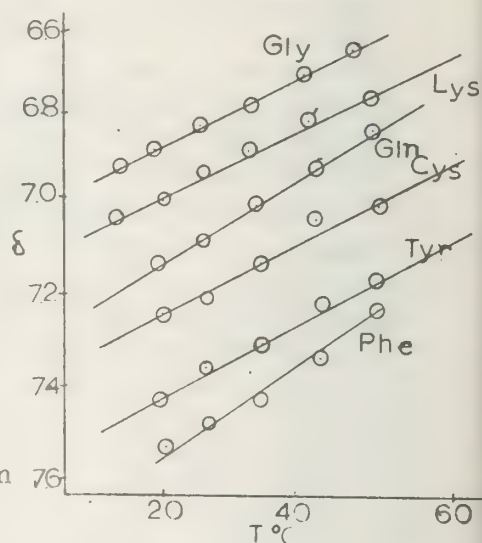


Figure 3: Chemical shift variation of N-H protons for lysine-vasopressin.

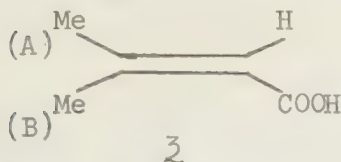


IV. THE SATURATION METHOD AND NUCLEAR OVERHAUSER ENHANCEMENTS

The saturation method allows one to measure the degree of solvation of solute protons. This is accomplished by monitoring intensities originating from exposed labile solute hydrogens exchanging rapidly with solvent. Usually, these resonances are diminished by transfer of saturation. In contrast, exposed nonexchangeable hydrogens are enhanced by a positive Nuclear Overhauser effect (NOE). Therefore, before a full description of the saturation method is presented, it is necessary to discuss the Nuclear Overhauser Effect.

The Nuclear Overhauser Effect (NOE)²⁴ is a change in the integrated nuclear magnetic resonance absorption intensity of a nuclear spin when the absorption of another spin is saturated. Essentially, three mechanisms may contribute to the observed NOE: (1) Direct dipole-dipole interaction or intermolecular dipole-dipole interaction. This manifests itself as an interaction between a solute resonance being observed and the solvent. The result of such an interaction is a positive NOE (increase in resonance intensity). (2) Dipole-dipole interaction between a monitored solute hydrogen and a nearby partially or completely saturated solute hydrogen. Such an interaction is defined as intramolecular and also results in a positive NOE: (3) Scalar coupling (J) between the monitored hydrogen and a solute hydrogen which is exchanging with the solvent at a rate comparable to the chemical shift difference between the two coupled solute nuclei. Unlike the two previous mechanisms, scalar coupling results in a negative NOE (decrease in resonance intensity). Anet²⁵ considered the case of

β_1 β -dimethylacrylic acid, 2, studied as a 9% solution in benzene- d_6 . The spectrum consisted of three multiplets: a septet due to H-2; a doublet with $J=1.3$ Hz due to one of the methyls, and another doublet with $J=1.3$ Hz due to the other methyl. The $\Delta\delta$ for the methyls was 0.55 ppm and these resonances were separated by ca. 4 ppm from H-2. The



question was which methyl corresponded to the upfield doublet and which to the downfield doublet. The solution to the problem was obtained by NOE measurements, where one of the methyls was saturated (i.e., the population of the α and β spin states was equalized) while H-2 was observed. Irradiation of either of the methyls resulted in the reduction of the H-2 septet to a quartet. However, when the high field methyl was irradiated the integral of the H-2 resonance increased by 17%, whereas saturation of the low field methyl resulted in a 4% reduction in the intensity of the H-2 resonance. Since methyl A is closer to H-2 than methyl B the enhancement of the H-2 signal when the upfield doublet was saturated indicated that the upfield resonance was that of the methyl A protons.

The term saturation method was defined as the transfer of saturation from solvent nuclei to labile, exchangeable, solute nuclei. This causes a concomitant decrease in intensity for the resonance which exchanges. Transfer of saturation is governed by equation (1).²⁶ The α and β states

$$(M_O^\alpha - M_Z^\alpha)/M_O^\alpha = [T_{1\alpha}/(T_{1\alpha} + \tau_\alpha)] [(M_O^\beta - M_Z^\beta)/M_O^\beta] \quad (1)$$

refer to solute and solvent nuclei, respectively, which are chemically exchanging. $T_{1\alpha}$, τ_α , M_Z^α and M_O^α are the spin-lattice relaxation time, lifetime, observed magnetization and the equilibrium magnetization of the nucleus, respectively. $(M_O^\alpha - M_Z^\alpha)/M_O^\alpha$ is the fractional decrease in resonance intensity of the α resonance resulting from irradiation of the β resonance, whose intensity is diminished by a factor of $(M_O^\beta - M_Z^\beta)/M_O^\beta$. Complete saturation of the β state causes a fractional decrease of the α resonance equal to $T_{1\alpha}/(T_{1\alpha} + \tau_\alpha)$, which is significant only if the pseudo-first order rate constant for exchange of the nucleus, $1/\tau_\alpha$, is comparable to or greater than its relaxation rate, $1/T_{1\alpha}$.

As an illustrative example, the saturation method has been applied to the acyclic, naturally occurring, octapeptide angiotensin II, 4.²⁶

Asn-Arg-Val-Tyr-Val-His-Pro-Phe

4

Figure 4a shows the region of the spectrum of angiotensin II downfield from the water resonance, when saturation power was applied at 1200 Hz upfield from the solvent peak. Glickson, et al.,^{27,30} compiled resonance assignments utilizing previously described methods. Saturation of the water resonance yielded the spectrum shown in Figure 4b. Figure 4c shows the amplified difference between the solvent saturated and the off resonance irradiated spectra (Figure 4b minus Figure 4a). Negative peaks originated from solvent-exposed labile hydrogens experiencing transfer of saturation.

These resonances were assigned to Arg peptide NH, Asn trans-amide and Arg

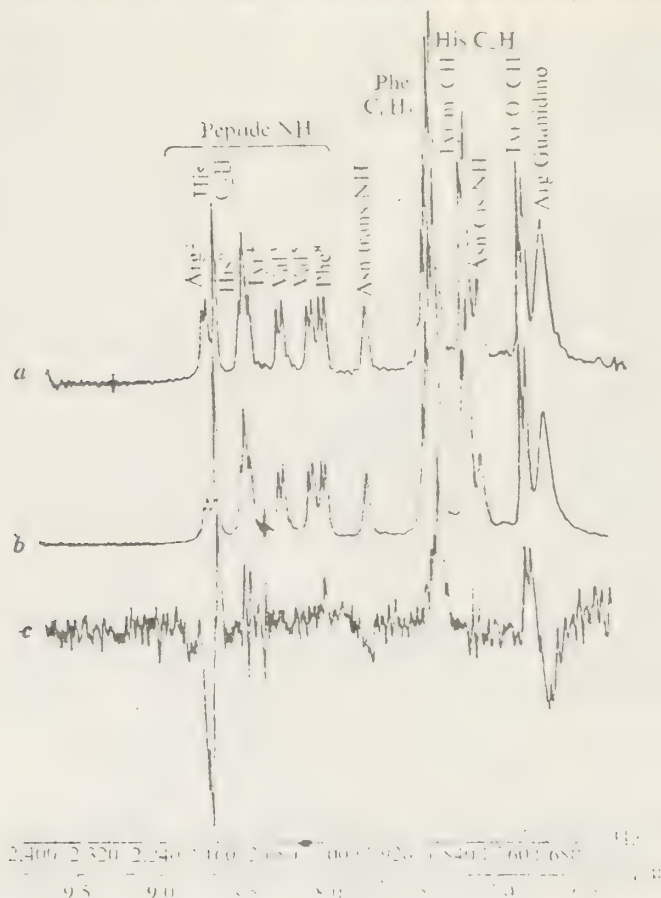


Figure 4: Spectrum of angiotensin II to low-field of water resonance.

guanidino NH's. The Arg peptide NH, Asn amide NH and Arg guanidino NH resonances decreased in intensity by 5%, 9% and 7%, respectively. Positive peaks originate from solute hydrogens experiencing a positive NOE. These resonances were assigned to the His 2-H and 4-H and the Tyr o-H. The His 2-H and Tyr o-H peaks experienced enhancements of 17% and 13%, respectively. Although the NOE's are considered to be non-instrumental, the authors did not minimize possible alternative relaxation pathways (e.g., by degassing the sample);^{32a} thus, the reported NOE's are very probably lowest limit values.

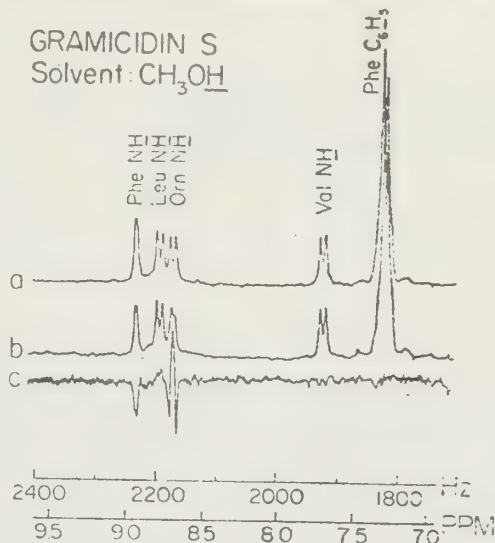
The observed transfer of saturation for NH protons of Arg is due to rapid exchange with solvent. This was interpreted to reflect that the Arg NH is well solvated. Partial saturation of the Asn trans-amide NH suggested that this hydrogen is also exposed to solvent. The sum of the data for Asn and Arg implied that the two N-terminal residues of angiotensin II are well solvated. This notion is substantiated by more "classical" methodology.^{9,17}

Observation of positive NOE's indicated that the dipolar mechanisms dominate exchange-modulated scalar coupling, which might be contributing to the relaxation of the His 2-H and 4-H and Tyr o-H protons. Therefore, these protons must be in intimate contact with the solvent and/or nearby exchangeable protons on the side chains of these residues must be substantially saturated as a result of rapid exchange with the solvent. In either case, a solvated environment is indicated for these CH protons, since dipolar relaxation depends on the inverse sixth power of the internuclear distance. Failure to observe an NOE for Tyr m-H protons indicates that this portion of the phenol group is not in contact with water. Although the substrate under

consideration had a well defined conformation, it is clear, nevertheless, that the saturation method easily delineates between exchangeable and non-exchangeable, solvated nuclei.

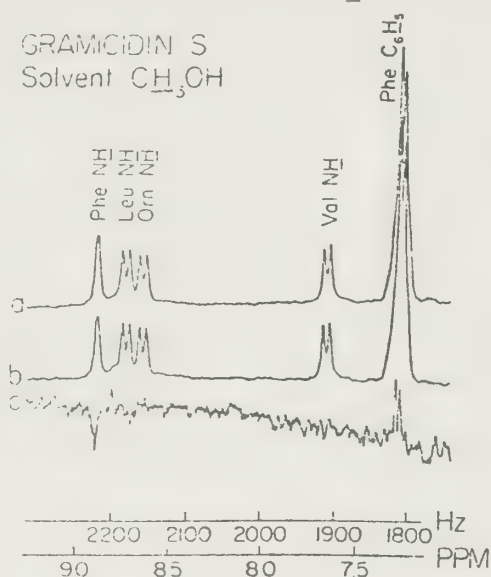
The conflicting reports for the conformational preferences of gramicidin S stem from an inability to assign unequivocally intramolecularly hydrogen bonded amide NH protons. Therefore, this case would seem ideally suited to test the capacity of the saturation method to distinguish those amide protons which are intramolecularly bonded from those which are not. Thus, the preferred solution conformation would be finalized.²⁷ Figure 5

Figure 5: Solvent saturation study of gramicidin S (5% w/v) in methanol at $30 \pm 1^\circ\text{C}$ showing the effect of saturation of the solvent OH resonance. Spectra were measured at 250 MHz by correlation spectroscopy (250 scans/spectrum; 1.6 sec/scan).



depicts the low field amide (N-H) proton region in methanol solvent. When the hydroxyl proton resonance of methanol is saturated, the intensity of the gramicidin S phenylalanine NH peak is decreased by 24%. This transfer of saturation results from rapid proton exchange between the methanol OH and phenylalanine NH groups. No significant changes in the intensity of other resonances were monitored. The distortion of the ornithine NH in Figure 5 results from partial decoupling of the $\alpha\text{-H}$, whose chemical shift is the same as that of methanol-OH. When the methyl resonance of methanol is saturated, (Fig. 6), the intensity of the phenylalanine C_6H_5 resonance

Figure 6: Solvent saturation study of gramicidin S in methanol showing the effect of saturation of the solvent CH_3 peak. Conditions are the same as in Figure 5 except that the CH_3 resonance rather than the OH resonance of methanol is saturated. The amplification factor in (c) is 5.



is increased by 5%; while the intensity of the phenylalanine NH peak is diminished 8%. The positive NOE experienced by the ring protons results from dipole-dipole interaction between solvent CH_3 protons and phenyl

protons. Since this dipolar coupling depends on the inverse sixth power and yet it is demonstrable, this requires intimate contact between hydrophobic phenylalanine ring and solvent methyl groups. The decreased intensity of the phenylalanine NH resonance, on the other hand, results from transfer of saturation from the methanol-OH proton, which is in rapid exchange with the phenylalanine NH proton. The methanol OH resonance decreases in intensity (not shown) by 22% upon saturation of the CH₃ peak, because the hydroxyl proton is relaxed by modulation of its scalar coupling.

Figure 7: Conformation of gramicidin S illustrating solvent exposed N-H protons.

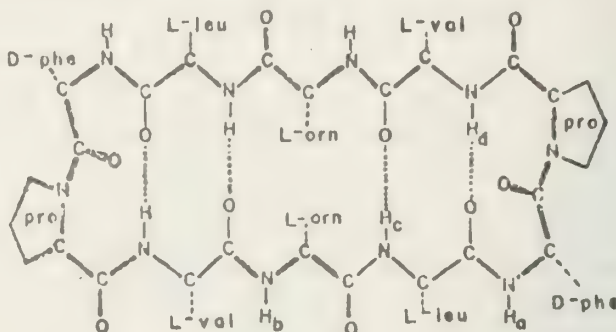


Figure 7 illustrates a portion of the proposed conformation of gramicidin S which is consistent with data obtained from the saturation experiment. Amide (N-H) protons from leucine (88.7), and valine (87.6) must be sequestered from solvent (as in H_c and H_d), since there is no detectable transfer of saturation and, therefore, they are considered to be intramolecularly hydrogen bonded. In contrast, since the phenylalanine amide (N-H) proton does evidence a decrease in its resonance intensity, it is clearly exposed to solvent (as in H_a). Due to the distortion of the ornithine resonance, no attempt was made to interpret the intensity data. Further, vicinal coupling constants measured for leucine, ornithine and valine amide (N-H) protons coupled to C α -H protons were 8.5 to 9.0 Hz.^{14,17} This reflected that the average (not necessarily the maximum) N-C α bond dihedral angles for these amino acids were different from that of phenylalanine, which showed almost no (>2 Hz) coupling. Model studies on simple N-methyl amides showed that average vicinal coupling constants are approximately 5 Hz, assuming relatively free rotation about the N-CH₃ axis. It might be expected that rotation about the N-alkyl bond should be relatively more restricted as the bulk of the alkyl substituent is increased. Indeed, dynamic NMR experiments have shown this^{32b} to be the case with a resulting increase in vicinal coupling (6.5 to 7.7 Hz); also, poly-L-alanine is known to have a trans NH-CH bond configuration with vicinal coupling equal to 6 Hz.^{32c} Therefore, it was concluded that small values for vicinal coupling correspond to large N-C α dihedral angles. The fact that the coupling in six of the eight possible amino acid residues is 8.5-9.0 Hz suggests strongly that their dihedral angles are small (ϕ about 30°, nearly cis), whereas the remaining two (phenylalanine) residues have dihedral angles which are large (ϕ about 150°, nearly trans). Finally, if models of gramicidin S are assembled with leucine and valine amide (N-H) protons intramolecularly hydrogen bonded the resulting dihedral angles yielded calculated²¹ coupling constants which were within experimental error of the measured vicinal coupling constants.

CONCLUSION

The utility of the saturation method is obvious. It permits one to ascertain unequivocally conformational preferences without recourse to physicochemical methods which perturb native solution conformations.

1. J. J. M. Rowe, J. Hinton and K. L. Rowe, *Chem. Rev.*, 70, 1 (1970).
2. K. D. Kopple and T. J. Schamper, in "Chemistry and Biology of Peptides", J. Meienhofer, ed., (Ann Arbor Publishers, Ann Arbor, Michigan, 1972), p 1.
3. R. S. Molday, S. W. Englander and R. G. Kallen, *Biochemistry*, 11, 150 (1972).
4. A. Huidt and S. D. Nielson, *Advances in Protein Chemistry*, 21, 287 (1966).
5. K. D. Kopple, M. Ohnishi and A. Go, *J. Am. Chem. Soc.*, 91, 4264 (1969).
6. M. Ohnishi and D. W. Urry, *Biochem. Biophys. Res. Comm.*, 36, 194 (1969).
7. T. P. Pitner and D. W. Urry, *Biochemistry*, 11, 4132 (1972).
8. R. Walter and J. D. Glickson, *Proc. Nat. Acad. Sci. U.S.A.*, 70, 1199 (1973).
9. K. D. Kopple and T. J. Schamper, *J. Am. Chem. Soc.*, 94, 3644 (1972).
10. T. D. Marinetti, G. H. Snyder and B. D. Sykes, *J. Am. Chem. Soc.*, 97, 6562 (1975).
11. J. D. Glickson, R. Rowan, T. P. Pitner, J. Dadok, A. A. Bothner-By, and R. Walter, *Biochemistry*, 15, 1111 (1976).
12. P. H. Von Dreele, A. I. Brewster, H. A. Scheraga, M. F. Ferger and V. du Vigneaud, *Proc. Nat. Acad. Sci. U.S.A.*, 68, 1028 (1971).
13. P. H. Von Dreele, A. I. Brewster, F. A. Bovey, H. A. Scheraga, M. F. Ferger and V. du Vigneaud, *Proc. Nat. Acad. Sci. U.S.A.*, 68, 3088 (1971).
14. A. Stern, W. A. Gibbons and L. C. Craig, *Proc. Nat. Acad. Sci. U.S.A.*, 73, 4 (1968).
15. F. A. Bovey, A. I. Brewster, D. J. Patel, A. E. Tonelli and D. A. Torchia, *Acc. Chem. Res.*, 5, 193 (1972).
16. P. H. Von Dreele, A. I. Brewster, J. Dadok, H. A. Scheraga, F. A. Bovey, M. F. Ferger and V. du Vigneaud, *Proc. Nat. Acad. U.S.A.*, 69, 2169 (1972).
17. (a) W. A. Gibbons, G. Nemethy, A. Stern and L. C. Craig, *Proc. Nat. Acad. Sci. U.S.A.*, 67, 239 (1970); (b) A. I. Brewster, V. J. Hruby, J. A. Glasel and A. E. Tonelli, *Biochemistry*, 12, 5294 (1973).
18. A. F. Casy, "PMR Spectroscopy in Medicinal and Biological Chemistry," Academic Press, New York, 1971.
19. R. G. Webb, M. W. Haskell and C. H. Stammer, *J. Org. Chem.*, 34, 576 (1969).
20. V. F. Bystrov, S. L. Portnova, U. I. Tsetlin, V. T. Ivanov and Yu. A. Ovchinnikov, *Tetrahedron*, 25, 493 (1969).
21. S. Sternhell, *Quart. Rev.*, 23, 236 (1969).
22. R. K. Gupta, J. A. Ferretti and E. D. Becker, *J. Magn. Res.*, 12, 275 (1974).
23. R. K. Gupta, J. A. Ferretti and E. D. Becker, *J. Magn. Res.*, 16, 505 (1974).
24. J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect," Academic Press, New York, 1971.
25. F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, 87, 5250 (1965).
26. T. P. Pitner, J. D. Glickson, J. Dadok and G. R. Marshall, *Nature*, 250, 582 (1974).
27. J. D. Glickson, J. Dadok and G. R. Marshall, *Biochemistry*, 13, 11 (1974).
28. T. Phil Pitner, J. D. Glickson, R. Rowan, J. Dadok and A. A. Bothner-By, *J. Am. Chem. Soc.*, 97, 5917 (1975).
29. J. Dadok and R. F. Sprecher, *J. Magn. Res.*, 13, 243 (1974).
30. H. E. Bleich, R. E. Galardy and M. P. Printz, *J. Am. Chem. Soc.*, 95, 2041 (1973).
31. Y. A. Ovchinnikov, V. T. Ivanov, V. F. Bystrov, A. I. Miroshnikov, E. N. Shepel, N. D. Abdullaev, E. S. Efremov and L. B. Senyavina, *Biochem. Biophys. Res. Comm.*, 39, 217 (1970).
32. (a) S. Berger, F. R. Kreissel and J. D. Roberts, *J. Am. Chem. Soc.*, 96, 4348 (1974); (b) L. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.*, 86, 337 (1964); (c) J. A. Schellman and C. Shellman, in "The Proteins", H. Neurath ed., (Academic Press, New York, 1964), vol. 2, 2nd ed., p 1.

APPLICATIONS OF LANTHANIDE SHIFT REAGENTS TO THE CONFORMATIONAL ANALYSIS OF LARGE MOLECULES

Reported by Peter L. Rinaldi

April 29, 1976

INTRODUCTION

Hinkley's first reported use of shift reagents involved the conformational analysis of cholesterol.¹ Since then a great deal has been published describing their uses.²⁻⁵

Changes in chemical shift (Δ values) are a result of the average shift of complexed and uncomplexed substrates in rapid equilibrium (Eq. 1). In organic solvents a lanthanide shift reagent (LSR) is usually a lanthanide(III) ion complexed to three β -diketonate ligands, and in aqueous solutions a lanthanide(III) chloride is commonly used. In order to observe a shift the substrate (S) must possess a functional group with some Lewis base character so that it can complex to the shift reagent (L).



For a molecule complexed to an LSR the paramagnetic shift of a nucleus is the sum of two terms, a contact (or through-bond) shift, and a dipolar (or through-space) shift (Eq. 2). Shift reagents have been used for many nuclei (e.g., ¹³C, ³¹P, ¹⁴N, ¹⁹F, ¹H). Contact shifts are negligible for ¹H nuclei unless the proton is bound directly to the shift reagent's complexation site, but other nuclei in general give significant contact shifts up to 4 or 5 bonds away from the complexation site.

$$\Delta_{\text{para}} = \Delta_{\text{contact}} + \Delta_{\text{dipolar}} \quad (2)$$

The dipolar shift is the sum of two terms, an axial and a non-axial term (Eq. 3), where r_i is the distance from nucleus i to the lanthanide metal (M), θ_i is the angle that the vector r makes with the principal magnetic axis of the metal, and ω_i is the angle the projection of r in the xy plane makes with the x axis (Fig. 1). In many instances the magnetic dipole can be assumed to be effectively axially symmetric, in which case the second term of Equation 3 vanishes to give Equation 4, the McConnell-Robertson equation.⁶ For the function of Equation 4 the sign of the shift inverts at 54.7°. Another assumption necessary is that a 1:1 complex between the shift reagent and the substrate is the major complex formed.

$$\Delta_{\text{dip},i} = K_{\text{ax}} (3\cos^2\theta_i - 1)/r_i^3 + K_{\text{nonax}} (\sin^2\theta_i - \cos 2\omega_i)/r_i^3 \quad (3)$$

$$\Delta_{\text{dip},i} = K(3\cos^2\theta_i - 1)/r_i^3 \quad (4)$$

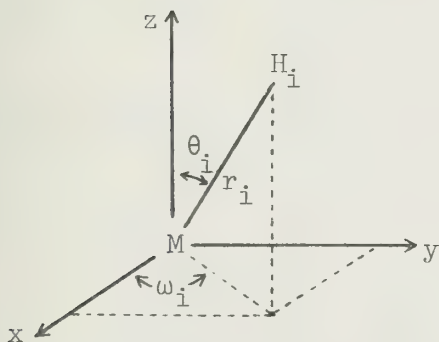


Fig. 1. Parameters for defining the position of a nucleus (H_i) relative to a metal ion (M).

Various computer programs have been written to analyze the data from a lanthanide shift experiment,⁷⁻¹² all of which use the same basic techniques with a few minor variations. The coordination center of the substrate is placed at the origin of the Cartesian coordinate system and the metal position is changed incrementally to produce good agreement of the calculated values with the experimental shifts of the protons nearest the binding site. Using standard bond lengths and bond angles the position of each nucleus in the substrate is defined and the shift for each nucleus is calculated for that conformation using

the McConnell-Robertson equation; new conformations are generated by incremental rotation about each successive rotatable bond and shifts are calculated for each of these new conformations.

Many functions are used to describe the error of a particular set of shifts for a given conformation, but by far the most widely used is the R-factor (Eq. 5) described by Willcott, Lenkinski, and Davis.¹¹ A value of zero for R corresponds to a perfect fit; anything up to 0.10 is acceptable, with values of about 0.04 being common. Use of this technique allows the utilization of the R-factor ratio test to determine the confidence levels of different solutions.

$$R = \left[\frac{\sum_i (\Delta_i^{\text{obs}} - \Delta_i^{\text{calc}})^2 w_i}{\sum_i (\Delta_i^{\text{obs}})^2 w_i} \right]^{\frac{1}{2}} \quad (5)$$

EXPERIMENTAL TECHNIQUES

Two approaches can be used to do the actual nmr experiment: the shift reagent can be added to the substrate kept at a constant concentration, or the substrate can be added to the shift reagent kept at a constant concentration. For substrate concentrations (S_0) much greater than shift reagent concentrations (L_0) the induced shift is given by Equation 6, where K_1 is the binding constant and Δ_1 is the bound chemical shift.

$$\Delta = K_1 L_0 \Delta_1 / (1 + S_0 K_1) \quad (6)$$

The first method is the more widely used, and involves adding shift reagent to substrate incrementally. When the substrate binds tightly to the shift reagent $K_1 S_0 \gg 1$ and Equation 6 simplifies to give Equation 7. The slope of the plot of Δ vs. L_0/S_0 then gives Δ_1 . For weakly binding substrates $1 \gg K_1 S_0$ and Equation 6 then simplifies to give Equation 8. The slope of the plot of Δ vs L_0/S_0 is no longer Δ_1 , but by taking ratios of shifts rather than absolute shifts, or by finding the binding constant by an independent experiment this problem can be alleviated. Theoretically, plots of this sort should resemble Fig. 2a; however, in practice, plots which deviate from linearity are obtained (Fig. 2b), since at low shift reagent concentrations, impurities scavenge the shift reagent, and at high concentrations 1:1 adducts may not be the only species that are formed.

$$\Delta = L_0 \Delta_1 / S_0 \quad (7)$$

$$\Delta = K_1 L_0 \Delta_1 = K_1 S_0 \Delta_1 (L_0 / S_0) \quad (8)$$

$$S_0 = \Delta_1 L_0 (\Delta)^{-1} - (L_0 + K_1^{-1}) \quad (9)$$

Alternatively, the method introduced by Armitage, et al.,¹³ can be used. Substrate is added incrementally to shift reagent; Equation 9 can then be written and from this it can be seen that a plot of S_0 vs. $1/\Delta$ will give a straight line with a slope of $\Delta_1 L_0$ and a y-intercept of $-(L_0 + K_1^{-1})$, thus giving

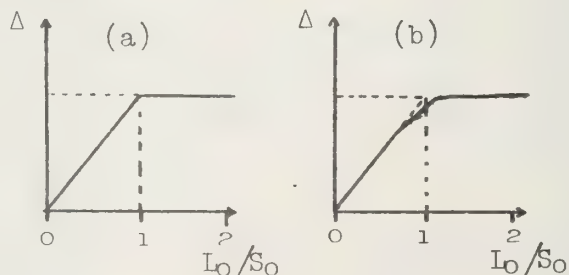


Fig. 2. Plots of L_0/S_0 vs. Δ (a) theoretical, and (b) experimentally observed.

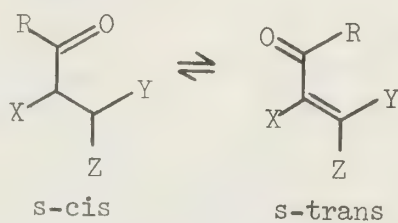
values of both K_1 and Δ_1 . An intrinsic advantage of this method is that it is insensitive to traces of water and other impurities that would bind to the shift reagent and give a non-linear plot at low I_0 in the first method.

CONFORMATIONAL ANALYSIS, SIMPLE SYSTEMS

Several criteria must be satisfied in order for the results from the following treatments to be valid: i) an average conformation of the substrate must be present which varies only slightly; ii) the fit must be to one averaged conformation and not to two or more highly populated conformations; iii) the shift reagent itself must not perturb the conformation of the molecule.

There are numerous reports of qualitative analysis of lanthanide induced shift (LIS) data applied to small, uncomplicated systems, for example to restricted rotation about single bonds of α,β -unsaturated carbonyl compounds (Scheme I).¹⁴⁻¹⁷

SCHEME I



Montando, et al.,¹⁸ have quantitatively determined the populations of s-cis and s-trans conformers (Scheme I) of a number of unsaturated aldehydes, ketones, esters and amides. The same calculation method was used for all of the above classes of compounds. Since these compounds are all rigid, optimal structures can be obtained simply by varying the position of the lanthanide metal (Ln, Fig. 3). Values of G_c and G_t , which correspond to the geometric term $((3\cos^2\theta-1)r^{-3})$ in Equation 4) for the s-cis and s-trans compounds, respectively, were calculated from atomic coordinates of the substrate obtained from Dreiding models, and values of R , Ω and ϕ . Solutions were obtained for each system by incrementally varying R , Ω , ϕ , and n_c (the mole fraction of s-cis), calculating a Δ_1 (Eq. 10) and computing the R-factor (Eq. 5).

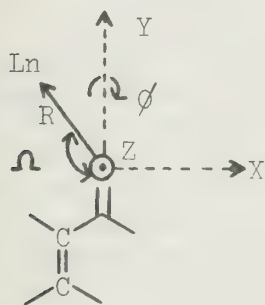


Fig. 3 The position of the Ln ion can be defined by three parameters, R , Ω , and ϕ .

the s-trans form, while cis- β -methyl substituted ketones ($R=\text{CH}_3$, $Y=\text{CH}_3$, $X=Z=\text{H}$ in Scheme I) prefer the s-cis form. Results were obtained for α,β -unsaturated amides, which indicate cis- β -unsubstituted amides prefer the s-cis arrangement, but α -methyl substituted amides prefer the s-trans conformation.

$$\Delta_i = K(n_c G_c + n_t G_t) \quad (10)$$

Their results show that methyl vinyl ketone and α -methyl substituted compounds ($R=\text{CH}_3$, $X=\text{CH}_3$, $Y=Z=\text{H}$ in Scheme I) prefer

Willcott and Davis¹⁹ reported the conformational analysis of a series of methoxyl xanthenes, 1, 2, 3, and 4, in which the methoxyl group can either be in the plane of the aromatic system or perpendicular to it. Figure 4 shows a plot of the shifts calculated from Equation 4 vs. the Ar-O-C dihedral angle; the horizontal line represents the experimentally observed shift. The results indicate that the methoxyl groups of 1 and 3 can either be perpendicular to the aromatic ring plane or exist in two equally populated, rapidly interconverting conformations with dihedral angles of 0° and 180° ; 2 contains the methoxyl group in the plane of the ring, and

4 gave anomolous results because the shift reagent formed a bidentate complex to the keto oxygen and the methoxyl oxygen.

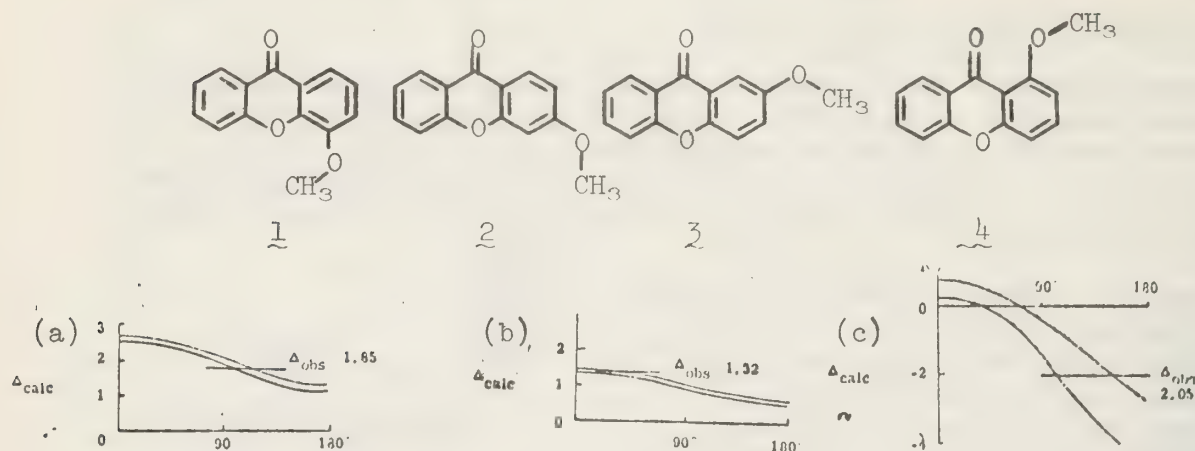


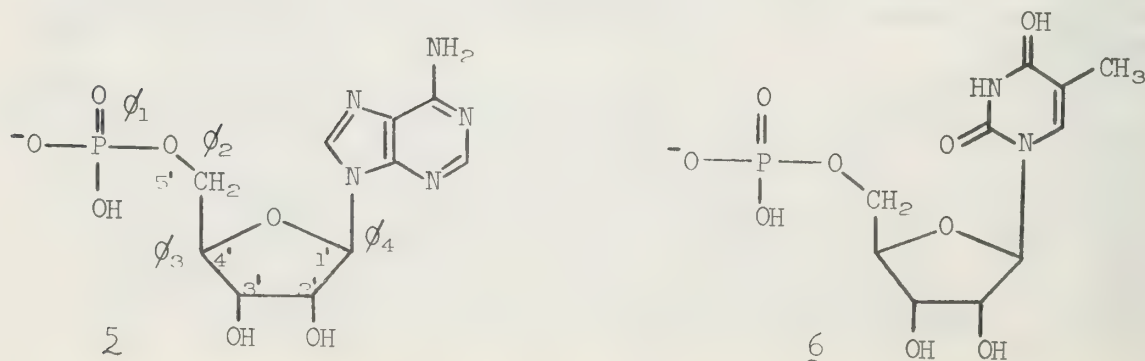
Fig. 4. Methyl shifts for: (a) 1, (b) 2, and (c) 3 plotted as a function of the Ar-O-C dihedral angle (conformations shown for 1, 2, and 3 are defined as O=O°).

Quantitative analysis of larger, more complicated systems has long been the object of a great deal of effort and this type of problem will be dealt with for the remainder of this seminar.

NUCLEOTIDES

Mono and dinucleotides have been the subject of extensive investigation. Barry and coworkers first applied their technique to the conformational analysis of adenosine-5'-monophosphate (5).^{20,21} They measured shifts due to several paramagnetic Ln(III) cations in deuterium oxide and used La(III) ion as a diamagnetic blank. Relative shifts for all protons were then determined and, since these were independent of the Ln(III) cation used, it was assumed that the paramagnetic field of the probe was axially symmetrical and that the shifts were pseudo-contact in nature (i.e., Eq. 4 is valid). Relaxation data can be obtained using Gd(III), which has a long electron relaxation time and an isotropic field associated with it. This ion induces line broadening described by Equation 11, where $\Delta\nu_{\frac{1}{2}}$ is the linewidth of the signal at half height, T_2 is the spin-spin relaxation time of the nucleus and r_i is the distance from the metal ion to nucleus i.

$$\Delta\nu_{\frac{1}{2}} \propto T_2^{-1} \propto r_i^{-6} \quad (11)$$



Shift experiments were performed at substrate concentrations below 0.03 M (above which stacking of the nucleotides is known to occur), and at pH values less than 2 in deuterium oxide. Shifts were not obtained in a control experiment with adenosine, but were obtained using ribose phosphate; thus, binding was occurring exclusively at the phosphate. Originally, binding of the Ln(III) ion was assumed to be to all three oxygens of the phosphate group (Fig. 5a), but no solutions were found for this model. A second coordination model (Fig. 5b), with the Ln(III) ion bound to two oxygens and in the plane of O_1-P-O_3 , was tested and found to be effective. Titration curves showed that only a 1:1 complex of shift reagent to nucleotide was formed in the concentration range of the experiment. All peaks were sharp, single lines, indicating rapid exchange of Ln(III) ion between the free and bound states. Shifts were calculated relative to those of the equivalent H-5' protons.

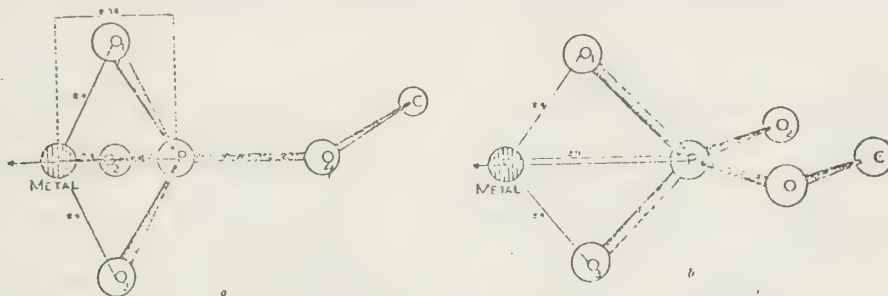


Figure 5. Binding of $\underline{5}$ to Ln(III) cation: (a) metal bound to all three oxygens and in line with the $P-O_4$ bond, (b) metal bound to two oxygens and in the plane of O_1-P-O_3 .

A starting geometry was then chosen from X-ray studies or, where no x-ray data were available, from molecular models using standard bond distances and bond angles, and calculated shift ratios were found for each nucleus. Using a computer and graphical display²² each bond was rotated by increments of 4° and shifts for each proton were calculated for that conformation. Certain conformations were rejected on the basis of constraints imposed by van der Waal's contacts and shift data. Of the several million conformations possible, all but 195 were rejected. Using relaxation data from Gd(III) line broadening this set was further narrowed down to 12 conformations, all belonging to the same family, with H-2' endo, a gauche conformation about the C-4'-C-5' bond, and the base anti to the sugar moiety (Figure 6). A similar treatment of thymidine monophosphate ($\underline{6}$) yielded 48 possible conformations, four of which belonged to a single family and were chosen on the basis of line broadening to be the best conformations.

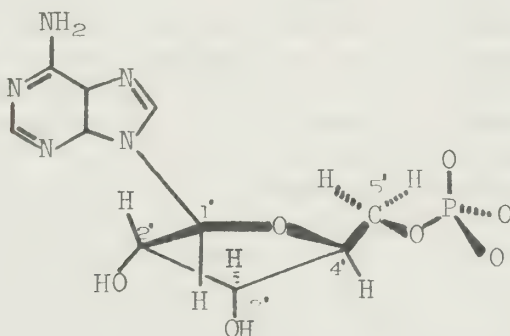
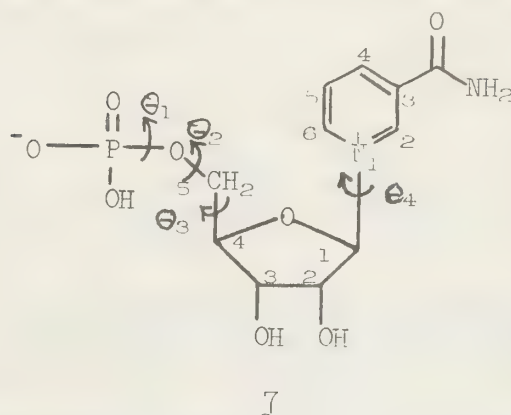


Figure 6. The solution conformation of AMP ($\underline{5}$).

Similar techniques have also been applied to other mononucleotides and to dinucleotides.²³⁻²⁸ Williams, *et al.*,²⁹ have used lanthanum(III) ethylenediaminetetraacetate complexes to obtain shift data on a number of the above nucleotides at biological pH. Their results show that conformations formed are similar to the ones found in the papers cited above at pH 2.

Bayley and Debenham³⁰ reported that the addition of Eu^{+3} to a number of nucleotides caused changes in their conformations, based on changes in circular dichroism (CD) spectra. Shifts of the isodichroic point of 2 to 5 nm to longer wavelength, and changes in the intensities of the CD bands of 30 to 50% were observed (*e.g.*, Figure 7). In considering these data the fact that these small differences become noticeable only at extremely high ratios of shift reagent to substrate (*e.g.*, in Figure 7 a ratio of 100:1) must be taken into account, whereas typical ratios for nmr experiments are 1:10 and ratios of 1:2 are rarely exceeded. Although the exact relationship between the perturbation of the CD spectrum and the change in conformation for these



compounds is not known, at these concentrations a 1:1 adduct may not be formed, and a second mole of Ln(III) ion may be binding to another basic site (*e.g.*, an aromatic nitrogen on the base), which would result in a change in the UV and therefore the CD spectrum.

Birdsall and coworkers³¹ have done an exhaustive study of the aqueous solution conformation of nicotinamide mononucleotide (NMN, I), a compound known to exist in multiple conformations. The usual LSR and broadening experiments were performed and, in addition, proton-proton and proton-phosphorus coupling constants were monitored. $J_{1'2}$ and $J_{4'5'}$ were invariable up to a two-fold excess of La^{+3} , indicating no change in the conformation of the ribose ring, and in the presence of a ten-fold excess of La^{+3} , $J_{5'p}$ remained constant, showing no dependence of the P-O-C-H dihedral angle in that region on the concentration of La^{+3} . If there were a change in the ratio of the *syn* and *anti* conformers of the nucleotide ring, the relative shifts of H-2 and H-6 would change on addition of shift reagent, a phenomenon not observed. Coupling constants showed a conformer ratio of 70% S (H-2' endo) to 30% N (H-3' endo) for the ribose ring, and H-4' gauche to the C-5' protons. LIS data fit the coupling constant data for the solutions either where $\theta_1 = 260^\circ$ for the S conformer and $\theta_1 = 115^\circ$ for the N conformer, or where free rotation about θ_1 was assumed (*i.e.*, an average of six conformers). Only one solution, which

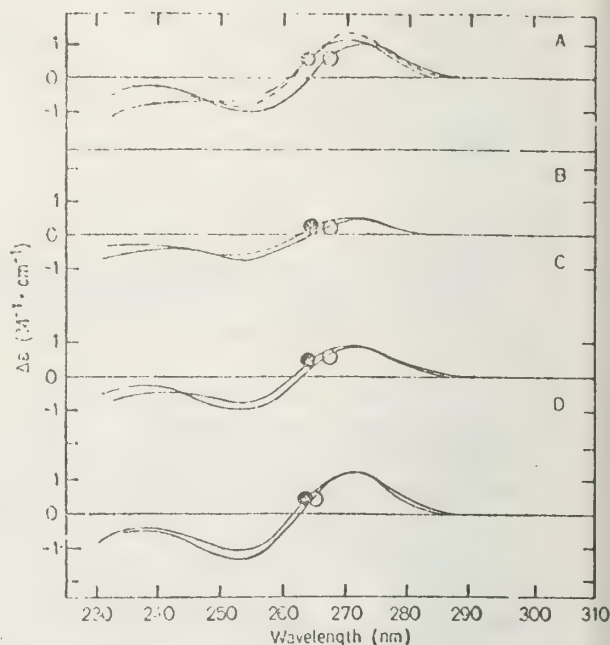
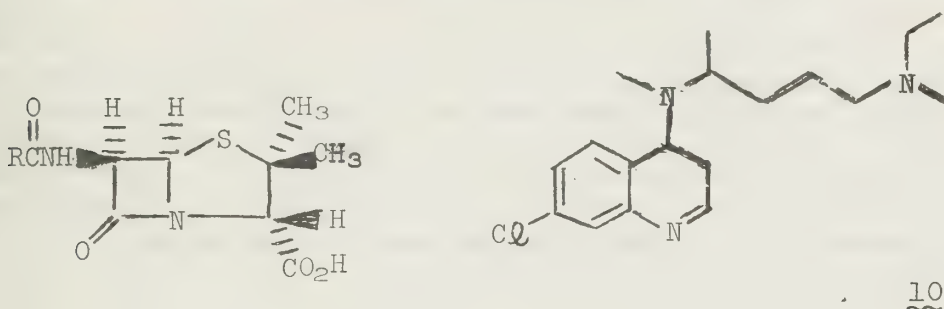


Fig. 7 Effect of lanthanides on the CD of NAD. [NAD] = 100 μM , 1-cm cuvette. (A) NAD (O), NAD + $[\text{Eu}^{3+}]$ = 10 mM (o), NAD + $[\text{La}^{3+}]$ = 10 mM (---). (B, C, D) NAD + $[\text{Eu}^{3+}]$ = 1 mM at 65 °C, 25 °C, 7 °C, respectively

consisted of a 2:1 ratio of the pyrimidine base syn (H-2' endo) to base anti (H-3' endo) fit all the experimental data, indicating a correlation between the syn/anti conformation and the ribose ring pucker. They concluded that shift and broadening data could give an incorrect solution for the conformation if coupling constants were not also taken into account to calculate a structure.

OTHER MOLECULES

X-ray crystallographic studies of ampicillin (8)³² and penicillin G (9)³³ have shown the existence of two different conformations of the thiazolidine ring in the solid state. As a result of their studies utilizing LSR, Williams and coworkers³⁴ have found that the two penicillins in solution both adopt the conformation of ampicillin in the solid state, possibly with an immeasurably small amount of the penicillin G conformation.



8 Ampicillin: R = C₆H₅CH₂NH-

9 Penicillin G: R = C₆H₅CH₂-

Angerman, et al.³⁵ have studied the solution conformation of the anti-malarial compound chloroquine (10); LaMar and Budd³⁶ have determined the solution conformation of Vitamin D using LSR. Delsarte and Weill³⁷ have used a shift reagent as a probe to study the helical conformation of poly(β -hydroxybutyrate).

The backbone conformation of valinomycin, a cyclic twelve membered depsipeptide which exhibits antibiotic activity, was studied by Servis and Patel³⁸. Conformations of small peptides have been studied by Levine and Williams.³⁹ It was shown by the measured contact shifts that binding occurred solely at the terminal carboxyl group. They found that binding of the carboxyl group of polyglycine to Tm(III) and Pr(III) differed, with one oxygen binding to the metal in the former, and two in the latter. It was also found that for (glycine)₅ the extended chain was formed on binding to Pr(III), but folding of the chain around the metal ion occurred when the peptide was bound to Tm(III). When the C-terminal amino acid possessed a large R group, back folding around the metal ion occurred to a larger extent. They explained this phenomenon on the basis of the more stable sphere of hydration of the Tm(III) ion as opposed to larger and smaller ions. A lyotropic series, which describes the denaturing power of certain ions, partly consists of the following: $\text{SCN}^{-2} > \text{NO}_3^{-} > \text{Cl}^{-} > \text{SO}_4^{-2}$. It was found that unfolding of the peptide chain with these ions occurred in the same order as the strength of the denaturant, with relatively straight chains obtained for SCN^{-} and less unfolding with SO_4^{-2} .

Treatments of shift data using an average of more than one conformation have been attempted;^{40, 41} however, if a molecule has more than one conformation significantly populated, shift data cannot be analyzed accurately utilizing the previously described treatments because of the relationship

described in Equation 12. Armitage, et al.,⁴¹ have written a program to

$$\Delta_i \propto \left\langle \frac{3\cos^2\theta_i - 1}{r_i^3} \right\rangle \neq \frac{3\cos^2\langle\theta_i\rangle - 1}{\langle r_i \rangle^3} \quad (12)$$

calculate shifts for a distribution of conformations using the first part of the relationship of Equation 12. It has been applied to a number of molecules, including 1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (11), aniline, and 12. The position of the lanthanide ion with respect to the donor atom can be defined by three variables, R , ω and ϕ (Figure 8). A plot of the R-factor contours varying these parameters was calculated. The best solution for 11 was obtained assuming a constant ϕ (i.e., no rotation about the C-2, O bond) and a static position of Eu(III). No acceptable solutions were obtained for 12, and aniline gave solutions for both free rotation about C-N and a static position at $\phi = 66^\circ$. Since H-2 and H-6 (or H-3 and H-5), opposite protons on the ring, are equivalent in the shift experiment the solution where $\phi = 66^\circ$ is clearly incorrect. This exemplifies the need to rely on other data in addition to lanthanide induced shifts, e.g., to use Gd(III) line broadening or coupling constants.

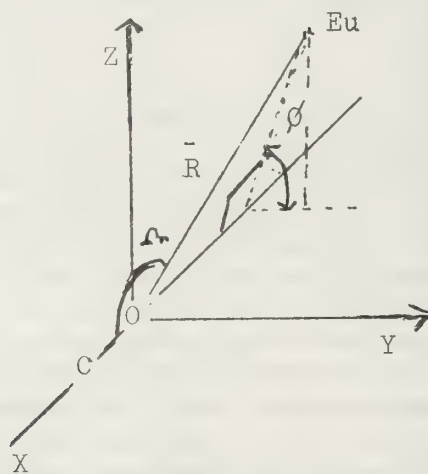
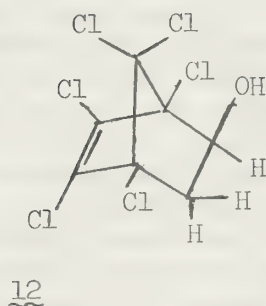
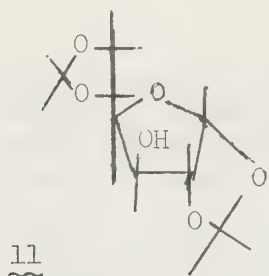


Figure 8. The position of an LSR relative to the donor atom can be described by three parameters, R , ϕ and ω .

Work has been described utilizing porphyrin complexes as shift reagents.⁴²⁻⁴⁴ In general, they do not give shifts as large as β -diketonate La(III) complexes, but in some instances they are specific in their binding; e.g., iron(II) tetraphenylporphyrin binds selectively to unhindered amines.⁴² Metal porphyrin moieties are found in many naturally occurring

molecules and, thus, can be used as internal shift reagents. Williams and coworkers⁴⁵ have proposed a structure for cytochrome c₃, a tetrahaem protein, on the basis of their qualitative analysis of the shifts obtained for different oxidation states of the four iron atoms in the molecule.

Metal ions bind to specific sites on certain large biological molecules, but, in general, when trying to extend this method to most very large molecules, identifying the binding site becomes a problem. Sykes⁴⁶ has described some preliminary work on the use of nitrotyrosine as a specific binding site, but much more work needs to be done in this area.

Conclusion:

The techniques described here are valuable for the determination of molecular conformation but a great deal of caution must be exercised in analyzing the data from shift experiments, and data should correlate with other experiments or an erroneous result can be obtained.

References:

1. C. C. Hinkley, J. Am. Chem. Soc., 91, 5160 (1969).
2. O. Hofer, in "Topics in Stereochemistry", Vol. 9, E. L. Eliel, Ed; J. Wiley and Sons, New York, N. Y., 1976.
3. R. E. Sievers, "Nuclear Magnetic Shift Reagents", Academic Press, New York, N. Y., 1973.
4. D. L. Sikkenga, Organic Chemistry Seminar, U. of Illinois, 28 (1974).
5. R. J. Convers, ibid., 162 (1971).
6. H. M. McConnell and R. E. Robertson, J. Chem. Phys., 29, 1361 (1958).
7. H. L. Ammon et al., J. Am. Chem. Soc., 95, 1968 (1973).
8. J. D. Roberts et al., J. Am. Chem. Soc., 95, 1659 (1973).
9. J. W. ApSimon et al., Can. J. Chem., 51, 3874 (1973).
10. A. D. Trifunac and J. J. Katz, J. Am. Chem. Soc., 96, 5233 (1974).
11. M. R. Willcott, III, R. E. Lenkinski, and R. E. Davis, J. Am. Chem. Soc., 94, 1742 (1972).
12. C. D. Barry et al., J. Mol. Biol., 84, 471 (1974).
13. I. Armitage et al., Can. J. Chem., 50, 2139 (1972).
14. C. Ceder and B. Beijer, Act. Chem. Scand., 26, 2977 (1972).
15. G. Montaudo et al., Tetrahedron, 29, 3915 (1973).
16. C. Beauté, Z. W. Wolkowski and N. Thoai, Chem. Comm., 700 (1971).
17. C. Beauté, et al., Tetrahedron Lett., 2473 (1971).
18. G. Montaudo, V. Librando, S. Caccamese and P. Maravigna, J. Am. Chem. Soc., 95, 6365 (1973).
19. Ref. 3, p. 159.
20. C. D. Barry, A. C. T. North, J. A. Glassel, R. J. P. Williams and A. V. Xavier, Nature, 232, 236 (1971).
21. C. D. Barry et al., J. Mol. Biol., 84, 471 (1974).
22. C. D. Barry et al., Fed. Proc., 33, 2368 (1974).
23. C. D. Barry et al., J. Chem. Soc., DA, 1765 (1974).
24. C. D. Barry et al., J. Mol. Biol., 84, 491 (1974).
25. D. K. Lavalley and A. H. Zeltmann, J. Am. Chem. Soc., 96, 5552 (1974).
26. G. R. Penzer, Eur. J. Biochem., 14, 162 (1974).
27. R. J. P. Williams et al., Eur. J. Biochem., 57, 135 (1975).
28. C. D. Barry et al., Biochem. Biophys. Acta, 262, 101 (1972).
29. C. M. Dobson, R. J. P. Williams, and A. V. Xavier, J. Chem. Soc., DA, 1762 (1974).
30. P. Bayley and P. Debenham, Eur. J. Biochem., 43, 561 (1974).
31. B. Birdsall et al., J. Am. Chem. Soc., 97, 2845 (1975).
32. M. N. G. James, D. Hall and D. C. Hodgkin, Nature, 220, 168 (1968).

33. G. J. Pitt, *Acta Cryst.*, 5, 770 (1952).
34. R. J. P. Williams et al., *J. Chem. Soc.*, F II, 71, 1145 (1975).
35. N. S. Angerman et al., *J. Am. Chem. Soc.*, 94, 7137 (1972).
36. G. N. LaMar and D. L. Budd, *J. Am. Chem. Soc.*, 96, 7317 (1974).
37. J. Delsarte and G. Weill, *Macromolecules*, 7, 343 (1974).
38. K. L. Servis and D. J. Patel, *Tetrahedron*, 31, 1359 (1975).
39. B. A. Levine and R. J. P. Williams, *Proc. R. Soc. Lond.*, A, 345, 5 (1975).
40. R. M. Wing, J. J. Uebel and K. K. Andersen, *J. Am. Chem. Soc.*, 95, 6046 (1973).
41. I. M. Armitage et al., *J. Am. Chem. Soc.*, 95, 1437 (1973).
42. J. E. Maskasky and M. E. Kenney, *J. Am. Chem. Soc.*, 95, 1443 (1973).
43. C. D. Barry et al., *Proc. R. Soc. Lond.*, A, 334, 493 (1973).
44. C. P. Wong, R. F. Venteicher and W. D. Horrocks Jr., *J. Am. Chem. Soc.*, 96, 7149 (1974).
45. R. J. P. Williams et al., *Nature*, 249, 425 (1974).
46. T. D. Marinetti, G. H. Snyder and B. D. Sykes, *J. Am. Chem. Soc.*, 97, 6562 (1975).

CONFORMATIONAL ANALYSIS OF 1,3,2-DIOXAPHOSPHORINANES

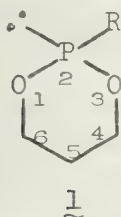
Reported by Charles Boeder

May 3, 1976

INTRODUCTION

The actual shape of a molecule in solution or solid phase is important in any thorough study of a chemical system. Barton, in landmark work of the early 1950's¹ demonstrated important relationships between conformation and reactivity, and conformational studies of cyclohexyl systems are numerous.² Of late, however, other six-membered rings have been investigated,^{3,4,5} and among these are 1,3,2-dioxaphosphorinanes.

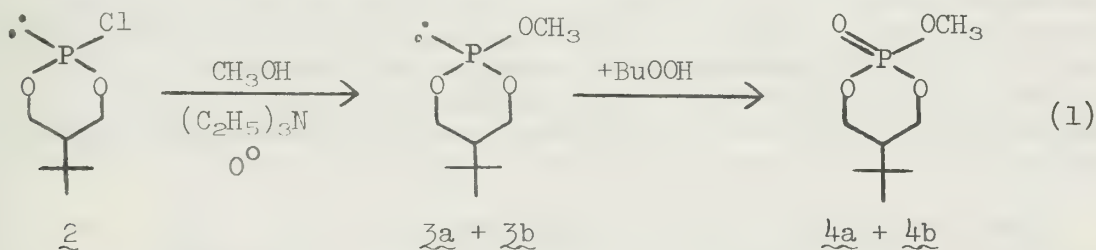
1,3,2-Dioxaphosphorinanes are saturated heterocycles with the general structure 1. This ring system differs from other six-membered rings subjected to conformational analysis. The P-O bond is longer than C-O bonds, and the O-P-O bond angle, known in pentavalent phosphorus compounds to be smaller than the O-C-O bond angle,⁶ is likely to be smaller in 1,3,2-dioxaphosphorinanes also. These two factors would create a slight "flattening" of the phosphorus end of this ring system in the chair or boat conformer. As an oxygen heterocycle, this ring is also affected by non-bonded electron pairs,⁵ while the phosphorus atom contains an electron pair as one substituent, rather than a proton or other group as in 1,3-dioxanes or 1,3-dithianes.



Conformational analysis has determined that the ring structure of 1,3,2-dioxaphosphorinanes may vary among chair, boat or twist conformers. Conformational mobility has often been retarded by the use of "locking groups," such as 5-tert-butyl, 4,6-dimethyl, or 4-methyl, all preferring the equatorial orientation since their axial orientation would lead to unfavorable steric interactions in the chair conformer. Isomerism at phosphorus, leading to an equatorial or axial preference depending on the substituent, has been successfully investigated by the methods reported here.

RING CONFORMATIONS OF 1,3,2-DIOXAPHOSPHORINANES

Bentrude, et al., have employed proton-proton and proton-phosphorus coupling constants to assign conformations to 5-tert-butyl-1,3,2-dioxaphosphorinanes, 3a and 3b.⁷ The reaction of phosphorochloridite 2 with methanol in the presence of triethylamine at 0° (Eq. 1) gave an overall yield of 93% (3a : 3b : 9 : 1). Heating above 80°, standing for several days at room temperature, or the addition of a trace of acid lead, however, to an equilibrium mixture (3a : 3b : 1 : 11).



Solution conformations for these systems can most readily be deduced from NMR analysis. For compounds 3a and 3b the spectra were first approximated as an ABXY system with the methine proton and phosphorus being X and Y, respectively. The analysis was carried out by computer simulation of

spectra,^{10,11} with a reported error in J of + 0.2 Hz. The coupling constants J_{AX} , J_{BX} , J_{AY} , and J_{BY} (Table I) are all vicinal (three-bond)

Table I. Vicinal Coupling Constants of Some 1,3,2-Dioxaphosphorinanes

Compound	$^3J_{AX}$	$^3J_{BX}$	$^3J_{AY}$	$^3J_{BY}$
<u>3a</u>	11.9 (Hz)	3.7 (Hz)	2.89 (Hz)	11.0 (Hz)
<u>3b</u> (37°)	4.65	4.91	5.03	8.40
(-62°)	4.10	3.10	3.90	9.40

couplings. The magnitude of the proton-proton coupling constants is related to the dihedral angle, ϕ , by the Karplus relationships.¹² A less extensive body of evidence indicates vicinal proton-phosphorus coupling obeys a similar rule.¹³

Substitution of deuterium for the methine proton of 3a differentiated H_A and H_B (Figure 1) by eliminating the large coupling, J_{AX} , and the small coupling, J_{BX} .

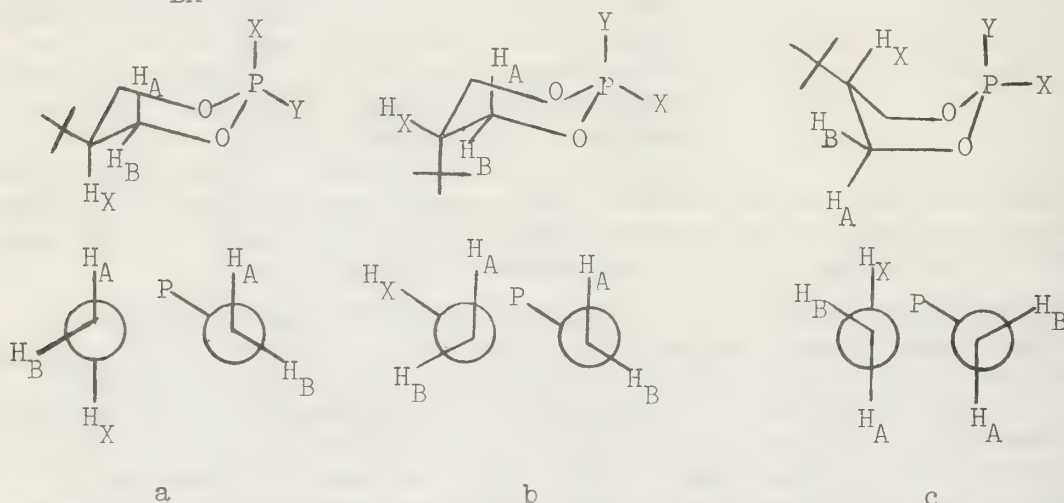


Figure 1. Possible ring conformations of 5-tert-butyl-2-R-1,3,2-dioxaphosphorinanes

From the Karplus relationship the large coupling constant (J_{AX}) indicates a trans-diaxial orientation of H_A and H_X and the small J_{BX} an axial-equatorial arrangement of H_B and H_X , an arrangement only possible for an equatorial tert-butyl group.

The coupling constants, J_{AY} and J_{BY} further confirm the chair conformation a above. The small J_{AY} is expected from the ca. 60° dihedral angle made between the axial H_A and phosphorus in the chair conformer. The equatorial H_B , on the other hand, with a dihedral angle of ca. 180° , is expected to give a large coupling constant. These data for 3a, the cis isomer (see section on stereochemistry about P) indicate conformation a of Figure 1. Chair conformer b is not considered because of J_{AX} . Boat conformers with tert-butyl in the equatorial position, such as c, or rapidly equilibrating twist forms would give nearly equal values of J_{AY} and J_{BY} .¹⁴

Verkade, et al., have investigated the series of compounds 5-8 (Table II).¹⁹ All of the compounds shown exhibit no appreciable spectral change from -40°

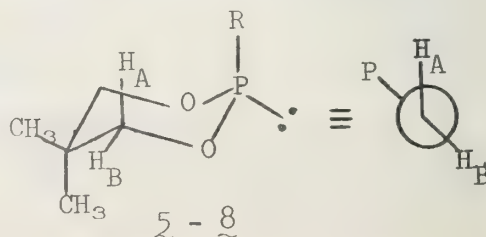
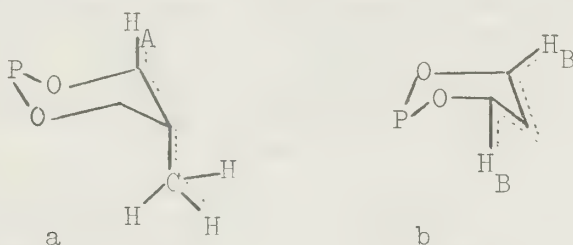


Table II. Vicinal Proton-Phosphorus Coupling Constants for a Series of 5,5-Dimethyl-2-R-1,3,2-dioxaphosphorinanes

Compound	R	$^3J(\text{POCH}_A)$	$^3J(\text{POCH}_B)$
5	OC_6H_5	2.8 Hz	10.8 Hz
6	OCH_3	2.8	10.8
7	F	2.8	10.8
8	Cl	6	10.8

to 160° , indicative of a single conformation.³⁴ The ^1H NMR spectra show two sets of methylene protons, a set at lower field (H_A and H_A') coupled to protons of the axial C-5 methyl, $^4J(\text{HCCCH}) \approx 0.8$ Hz and a higher field set (H_B and H_B') coupled to each other, $^4J(\text{HCCCH}) \approx 2.5$ Hz. Long range four-bond interproton coupling has been shown to be enhanced by a planar "W" arrangement of the bonding path.²¹ The planar "W" bond path explains both observed couplings. With H_A and H_A' axial, a "W" bonding path as shown in a of Figure 2 can account for the coupling observed with the axial C-5 methyl which is not observed for the equatorial methylene protons. A "W" bond path is also present for the equatorial methylene protons as seen in b. These data do not differentiate between the chair and boat conformers shown. Further

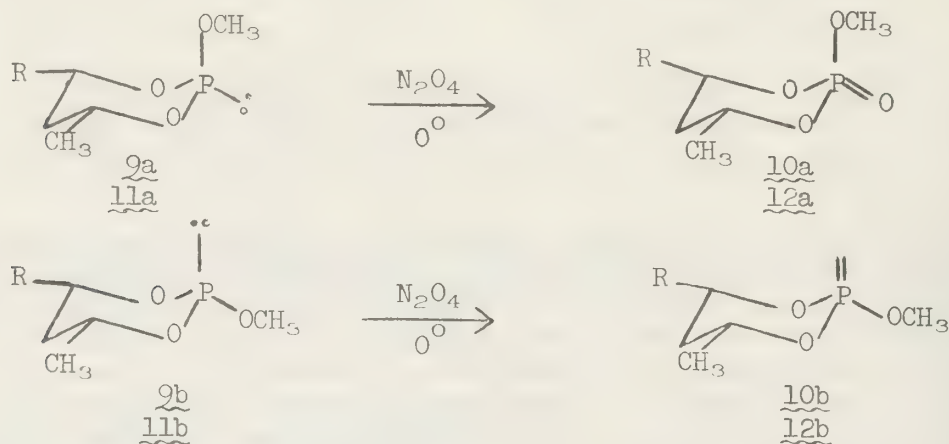
Figure 2. "W" coupling paths for $J(\text{H}_A\text{CCCH}_3)$ and $J(\text{H}_B\text{CCCH}_B')$

analysis reveals that H_A and H_A' couple to phosphorus less (3 Hz) than the equatorial H_B and H_B' (10 Hz), indicating chair conformer a (see also 5-8). The long range interproton coupling constants rule out unsymmetrical boat or twist boat conformers, in which $J(\text{HCOP})$ would be comparable for H_A and H_B due to similar dihedral angles.

Stereochemistry about Phosphorus of 2-Alkoxy-1,3,2-dioxaphosphorinanes

Oxidation of phosphites 3a and 3b with tert-butyl hydroperoxide gave phosphates 4a and 4b, respectively. Oxidation is believed to proceed with retention of configuration at phosphorus, since optically active phosphines oxidize with retention of configuration.⁸ Dipole moment data provide further evidence for retention of configuration upon oxidation.²⁶ Dipole moments of 2-alkoxy-2-oxo-1,3,2-dioxaphosphorinanes would be expected to be larger for axial alkoxy and equatorial oxygen, for the dominant $\text{P}=\text{O}$ dipole would align with the ring C-O dipoles. This was shown experimentally for 4,6-dimethyl-2-methoxy-2-oxo-1,3,2-dioxaphosphorinanes 10a and 10b ($\text{R}=\text{CH}_3$), derived from nitrogen tetroxide oxidation of 9a and 9b ($\text{R}=\text{CH}_3$) as seen in Figure 3. Compound 10a has the larger dipole moment (6.11D) and 10b the smaller (4.69D), as expected if oxidation proceeds with retention.

Various isomeric mixtures of 3a and 3b oxidized to their phosphates gave the same isomeric phosphate ratio as that of the starting phosphite ratio, indicating high stereoselectivity. Analysis of the geometry of phosphates 4a and 4b would then give the geometry of 3a and 3b. Phosphate 4b was shown by X-ray analysis to be trans, in the chair conformation, and with both tert-butyl and methoxy substituents equatorial.⁷ A similar argument to obtain geometry of 3a and 3b, using a stereospecific phosphonate formation with methyl iodide, in which equal ratios of starting phosphites and



product phosphonates were obtained, again indicated 3b to be trans. Retention of configuration at phosphorus was also expected here, since the reaction takes place where the phosphorus non-bonded electron pair is most exposed.⁹ These stereochemical analyses indicated that 3b, the thermodynamically less stable isomer, is trans and 3a is cis.⁷

³¹P and ¹³C nuclear magnetic resonance techniques are often employed to complement ¹H NMR of 1,3,2-dioxaphosphorinanes.^{7,15,16,17} It should be noted that, although generalizations from one system to another concerning the magnitude of the chemical shift changes in ¹³C NMR can be misleading, the direction of shift is informative. For the purpose of conformational analysis of six-membered rings, the steric compression shift is most important. The effect of steric compression on a carbon is to shift its ¹³C nuclear magnetic resonance upfield. This effect is seen in an upfield shift of carbons-1,3, and 5 of axial methylcyclohexanes relative to resonances of the equatorial methyl or unmethylated systems, since axial-3,5 hydrogens' interaction with the axial methyl causes steric compression.¹⁸

	Atom, comp	¹³ CH ₃ -O	¹³ C ₄	¹³ C ₆	¹³ C ₅	¹³ CH ₃	³¹ P
<p>13a</p>	Δδ, ppm	+1.2	-4.0	-4.0	+1.9	-0.8	-4.3
<p>13b</p>							

Figure 4. ¹³C and ³¹P NMR shifts with change in configuration at phosphorus

Compounds 13a and 13b are known to be predominantly in the conformations shown in Figure 4.¹⁷ The figure represents the chemical shift change in ppm in going from 13a to 13b, with a negative number representing an upfield shift.¹⁵ As can be seen, the effect of an equatorial to axial methoxy change is to shift the C-4 and C-6 resonances to higher field. This steric shift is also seen in the ³¹P NMR spectra. Trivalent phosphorus is expected on theoretical grounds to show ¹³C NMR shift trends.^{15,20}

Characteristic δ-effects (δ to phosphorus) have been noted in spectra of some 1,3,2-dioxaphosphorinanes.¹⁵ It has been observed that equatorial δ-substituents cause an upfield shift of the ³¹P NMR signal (relative to the unsubstituted compounds).^{15,19} This shift was not appreciable for axial δ-substitution. The heteronuclear coupling, ⁴J(¹³CH₃-C-C-O-P), for cis-2-methoxy-5-methyl-1,3,2-dioxaphosphorinane (equatorial methyl, axial methoxy)¹⁵ and the 5,5-dimethyl analog,¹⁹ also shows specificity with ⁴J(¹³C_{eq}CCOP) = 1.3 Hz while the corresponding C-5 axial coupling was not observed. An equatorial 5-methyl has a W arrangement (although not planar), while the axial 5-methyl does not, possibly accounting for the observed specificity.¹⁵

Lanthanide induced shift studies have also been used as configurational probes.^{26,33} Lanthanide induced shifts (LIS) are greatest for those protons closest to the complexing lanthanide.³⁵ The shift reagent, complexing to the phosphoryl oxygen, makes the axial methylene protons sensitive to configuration at phosphorus, since an axial oxygen would cause the lanthanide, when complexing, to be closer to these protons than would an equatorial oxygen. Table III shows LIS studies for 12a and 12b (Figure 3) and 14a and 14b.²⁶ The larger LIS for axial H-4 and H-6 for 12b indicates an axial phosphoryl oxygen and an equatorial methoxyl, thus giving the configuration of the precursor phosphites.

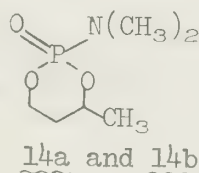
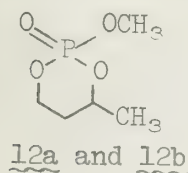


Table III. Lanthanide induced shifts for some 1,3,2-dioxaphosphorinanes

Δδ [- δ_{no Eu(fod)₃} + δ_{2 substrates} / Eu(fod)₃]

Compound	H ₆ (ax)	H ₆ (eq)	H ₅ (eq)	H ₅ (eq)	H ₄ (ax)
<u>12a</u>	2.3 (ppm)	1.6	1.5	2.6	2.3
<u>14a</u>	3.0	2.2	1.5	2.4	3.3
<u>12b</u>	4.6	2.2	1.4	2.8	5.3
<u>14b</u>	4.5	2.2	1.6	2.6	5.1

Measurement of dipole moments gives information concerning configuration at phosphorus. Bodkin and Simpson, in dipole studies on 16a and 16b (Figure 5), concluded, since the S = PO₃ moiety has the overriding dipole (~3.44D), that 16b would have the largest dipole. Thionophosphate 16a has a dipole moment of 3.19D, and 16b, 5.36D.²² Predicted values, based on C-O and C-H dipoles of 0.71 D and 0.40 D respectively, were 3.31 D for 16a and 5.78 D for 16b. Since the reaction giving the thionophosphates is known to go with retention of configuration at phosphorus,²³ any conclusions concerning configuration at phosphorus for 16a and 16b also apply to 15a and 15b. The thermodynamically more stable isomer, 15b, because of its thionophosphate's higher dipole, is concluded to have an axial ethoxyl group. This technique

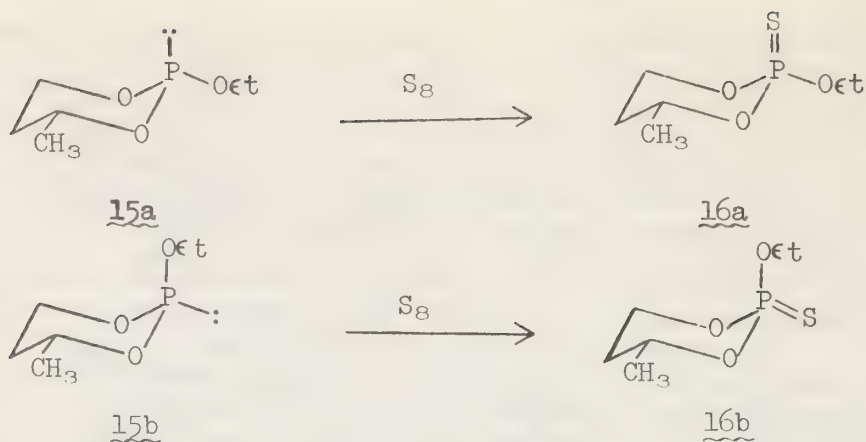


Figure 5. Reaction of 1,3,2-dioxaphosphorinanes with sulfur.

was further extended to include methoxyl and propoxyl, both showing an axial preference.²⁴ Verkade has used dipole measurements on borane adducts to 1,3,2-dioxaphosphorinanes to conclude axial preference of methoxyl.²⁵

Stereochemistry about Phosphorus of 2-Amino-1,3,2-dioxaphosphorinanes

Although the majority of 2-R-1,3,2-dioxaphosphorinanes studied showed an axial preference, amino substituents are not as predictable. Verkade and Mosbo²⁶ have shown the thermodynamically stable isomer (90% at equilibrium) of 2-dimethylamino-4,6-dimethyl-1,3,2-dioxaphosphorinane has the amino substituent in the equatorial position. Analysis of the isomeric 2-amino-1,3,2-dioxaphosphorinanes was carried out on their 2-oxo derivatives from nitrogen tetroxide oxidation (Figure 6). Dipole moment methods, described earlier, were employed. Compound 18a, derived from the more stable isomer,

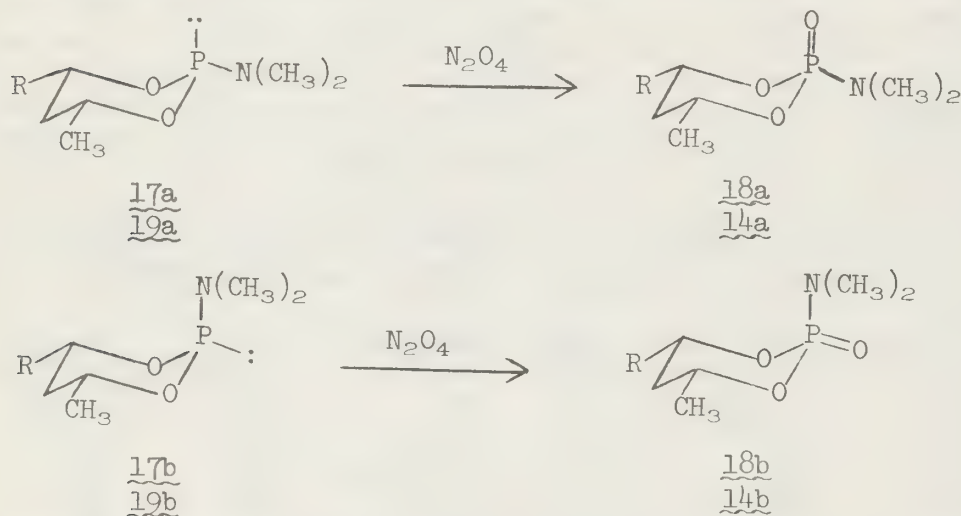


Figure 6. Retentive oxidation of 2-amino-1,3,2-dioxaphosphorinanes (17 and 18, R = CH₃; 19 and 20, R = H)

has a lower dipole moment (4.05 D) than 18b (5.80 D), indicating that 18a (ergo 17a) has an equatorial dimethylamino group.

LIS studies also inferred equatorial dimethylamino preference (see Table III).²⁶ Similar LIS analysis showed an equatorial dimethylamino group in the more stable isomer of 2-dimethylamino-5-tert-butyl-1,3,2-dioxaphosphorinane, 20a.³³

Compounds 20a and 20b were made by the reaction of tris(dimethylamino)-phosphine with 2-tert-butyl-1,3-propanediol (Eq. 2).³³ ¹H NMR analysis of the isolated products showed a 61:39 ratio of 20a to 20b. Oxidation at 5° with nitrogen tetroxide gave the 2-oxo compounds, 21a (60%) and 21b (40%). At room temperature 20a and 20b equilibrate to 83% of 20a, a percentage that decreases upon heating, increases with cooling, and returns to 83% at room temperature. The ¹H NMR analysis, carried out with computer assistance,¹³ is given in Table IV; it suggests a chair conformation for 20a and 21a, with the tert-butyl group, equatorial.

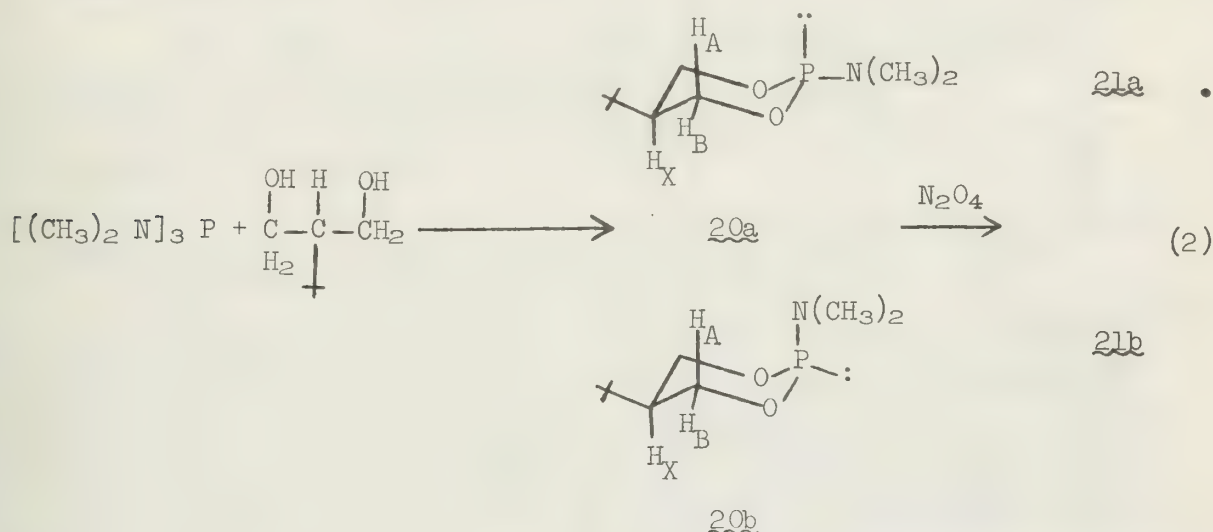


Table IV. Vicinal coupling constants of 2-amino and 2-amino-2-oxo derivatives

Compound	J_{AX}	J_{BX}	J_{AP}	J_{BP}
<u>20a</u>	10.68 Hz	4.08 Hz	2.50 Hz	19.62 Hz
<u>21a</u>	11.57	4.06	2.34	21.37
<u>21b</u>	10.18	4.80	8.68	13.70

Bentrude further notes that for 20a and 21a $^3J_{BP}$ is about double that of 1,3,2-dioxaphosphorinanes in which the phosphorus substituent is known to be axial in the chair conformer.^{7,19,29} A similar large coupling ($^3J_{BP} = 19.8$ Hz) is observed for trans-2,5-di-tert-butyl-1,3,2-dioxaphosphorinane, which, for steric reasons, has diequatorial substituents.²⁹ This large vicinal coupling has become indicative of an axial lone-pair in the chair conformer.

Recent work by Stec³² indicates that the equatorial preference of 2-amino-1,3,2-dioxaphosphorinanes is not general. 2-Anilino-4-methyl-1,3,2-dioxaphosphorinanes 22a and 22b equilibrate to 90% of the axial anilino isomer, 22a. This was shown experimentally by oxidation to the 2-oxo analogs 23a and 23b by tert-butyl hydroperoxide (Figure 7). Stec had previously shown the stereochemistry of 23a and 23b by chemical correlation and spectral evidence,^{36,37} and concluded 22a to be trans (axial 2-anilino). Spectral evidence further supports this, since the vicinal coupling constant, $^3J(H_6^{(eq)}COP) = 11.7$ Hz, is typical for an axial 2-R, and 22a exhibits a steric^(eq) δ -effect, the C-4 and C-6 resonances being shifted upfield relative to those of 22b, isolated under kinetic control.

Explanations of amino isomeric preferences vary.^{26,32,33,38} The anomeric effect,⁵ imposed to explain the axial preference for most 2-R-1,3,2-dioxaphosphorinanes, has been considered to be overshadowed by electron-pair interactions between nitrogen and ring oxygens.^{26,33,38} Steric arguments,

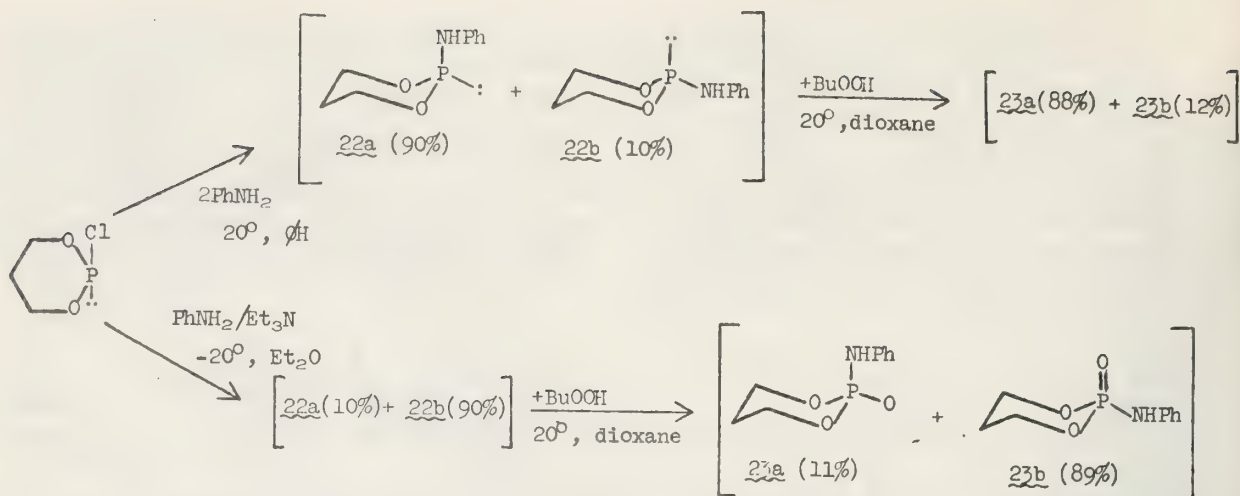


Figure 7. Kinetic and thermodynamic products from conformation of 2-anilino-2-methyl-1,3,2-dioxaphosphorinanes

that axial NR_2 substituents give an unfavorable 1,3 interaction with axial-C-4 and C-6 hydrogens, have also been proposed.³² Although this steric argument does explain why the anilino group is axial, significantly having a hydrogen on nitrogen to relieve 1,3 interactions, it does not explain the slight equatorial preference of the 2-methylamino group (55% equatorial at room temperature).³³ It is apparent that further experimental data are needed before a satisfactory explanation of the 2-amino-1,3,2-dioxaphosphorinane conformational preference can be understood.

Generalizations

Early conformational analysis of 1,3,2-dioxaphosphorinanes did not show general trends.^{19,27,28} However, as NMR analysis became more detailed, ambiguities were cleared up. Axial preference has now been established for halogen,^{19,29} alkoxyl,^{7,19,22,24} thioalkoxyl,³² alkyl,^{29,30} phenyl,^{29,30} thiophenoxyl¹⁹ and anilino³² groups. Equatorial preference has been seen for *tert*-butyl,²⁹ dimethylamino,^{26,33} and methylamino³³ groups.

Conformationally Mobile Systems

The conformational analysis of some 1,3,2-dioxaphosphorinanes, mostly those less thermodynamically stable isomers, indicates conformational mobility. These compounds are usually difficult to isolate, owing to rapid isomerization. ^1H NMR spectral interpretation is difficult due to overall averaging of the coupling constants of various conformers.

An example of a conformationally mobile system is *cis*-2-dimethylamino-5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane, **21b**.³³ Compound **21b** has values of $^3J_{\text{AP}}$ and $^3J_{\text{BP}}$ intermediate between the extremes known in the conformationally stable *trans* isomer ($^3J_{\text{AP}}$ and $^3J_{\text{BP}}$ are 8.68 and 13.70 Hz for *cis* vs 2.34 and 21.37 Hz for *trans*). This and spectral evidence of a conformational change with added lanthanide shift reagent suggest a mobile conformational equilibrium.³³

References

1. D. H. R. Barton, *Experientia*, **6**, 316 (1950).
2. J. A. Hirsch, in "Topics in Stereochemistry", Vol. 1, N. L. Allinger and E. L. Eliel, Eds., John Wiley and Sons, New York, N.Y., 1967, p. 199.

3. C. Romers, C. Altona, H. R. Buys, E. Havinga, in "Topics in Stereochemistry", Vol. 4, N. L. Allinger and E. L. Eliel, Eds., John Wiley and Sons, New York, N.Y., 1969, p. 39.
4. R. O. Hutchins, B. E. Maryanoff, J. P. Albrand, A. Cogne, D. Gagnaire, J. B. Robert, J. Am. Chem. Soc., 94, 9151 (1972).
5. E. L. Eliel, M. C. Knoeber, J. Am. Chem. Soc., 90, 3444 (1968), E. L. Eliel, W. F. Bailey, J. Am. Chem. Soc., 96, 1798 (1974).
6. M. U. Haque, C. N. Caughlan, J. H. Hargis, W. G. Bentrude, J. Chem. Soc., A, 1786 (1970).
7. W. G. Bentrude, J. H. Hargis, J. Am. Chem. Soc., 92, 7136 (1970).
8. D. B. Denney, W. H. Hanfin Jr., Tetrahedron Lett., 2177 (1963).
9. A. J. Kirby, G. Warren, in "The Organic Chemistry of Phosphorus", Elsevier, Amsterdam, 1967, pp. 37-45.
10. S. Castellano, A. A. Bothner-By, J. Chem. Phys., 41, 3863 (1964).
11. D. W. White, G. K. McEwen, R. D. Bertrand, J. G. Verkade, J. Mag. Res., 4, 123 (1971).
12. M. Karplus, J. Chem. Phys., 30, 11 (1959), J. Am. Chem. Soc., 85, 2870 (1963).
13. A. A. Bothner-By, R. H. Cox, J. Phys. Chem., 72, 1830 (1969).
14. F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969, p. 135.
15. M. Haemers, R. Ottinger, D. Zimmermann, J. Reisse, Tetrahedron, 29, 3539 (1969).
16. W. J. Stec, Z. Naturforsch., B, 29, 109 (1974).
17. W. J. Stec, A. Okruszek, J. Chem. Soc. Perkin I, 1828 (1975).
18. J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p. 112.
19. D. W. White, R. D. Bertrand, G. K. McEwen, J. G. Verkade, J. Am. Chem. Soc., 92, 7125 (1970).
20. B. E. Mann, J. Chem. Soc. Perkin II, 30 (1972).
21. S. Sternhill, Revs. Pure Appl. Sci., 14, 15 (1964).
22. C. Bodkin, P. Simpson, Chem. Commun., 829 (1969).
23. W. E. McEwen, in "Topics in Phosphorus Chemistry", Vol. 2, M. Grayson and E. J. Griffith, Eds., Interscience, New York, N.Y., 1965, p. 25.
24. C. Bodkin, P. Simpson, J. Chem. Soc., B, 1136 (1971).
25. D. W. White, G. K. McEwen, J. G. Verkade, Tetrahedron Lett., 5369 (1968).
26. J. A. Mosbo, J. G. Verkade, J. Am. Chem. Soc., 95, 4659 (1973).
27. D. Gagnaire, J. B. Robert, Bull. Soc. Chim. Fr., 2240 (1967).
28. J. P. Albrand, D. Gagnaire, J. B. Robert, M. Haemers, Bull. Soc. Chim. Fr., 3496 (1969).
29. W. G. Bentrude, H. W. Tan, K. C. Yee, J. Am. Chem. Soc., 97, 573 (1975).
30. W. G. Bentrude, K. C. Yee, Tetrahedron Lett., 3999 (1970).
31. W. G. Bentrude, K. C. Yee, R. D. Bertrand, D. M. Grant, J. Am. Chem. Soc., 93, 797 (1971).
32. A. Okruszek, W. J. Stec, Z. Naturforsch., B, 30, 430 (1975).
33. W. G. Bentrude, H. Tan, J. Am. Chem. Soc., 95, 4666 (1973).
34. R. A. Newmark, C. H. Sederholm, J. Chem. Phys., 39, 3131 (1963); 43, 602 (1965).
35. O. Hofer, in "Topics in Stereochemistry", Vol. 9, N. L. Allinger and E. L. Eliel, Eds., John Wiley and Sons, New York, N.Y., in press.
36. W. J. Stec, A. Lopusinski, Tetrahedron, 29, 547 (1973).
37. W. J. Stec, M. Mikolajczyk, Tetrahedron, 29, 539 (1973).
38. J. G. Verkade, Tetrahedron Lett., 3231 (1975).

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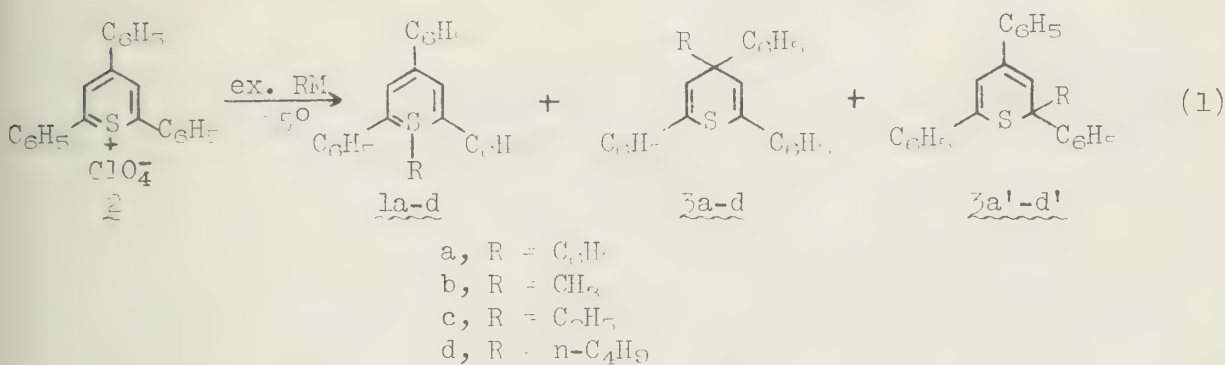
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INTRODUCTION

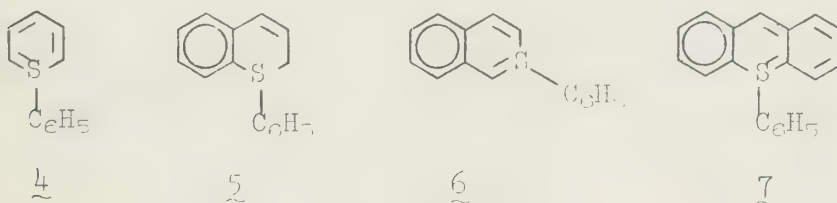
Thiabenzenes, thianaphthalenes, and thiaanthracenes can be viewed empirically as compounds in which one or more carbon atoms in the corresponding aromatic compounds have been replaced by tetravalent sulfur atoms. Considerable interest has been expressed recently in the type of bonding involved in these compounds and their potentially aromatic character.¹ Throughout this abstract, the term "thiabenzenes" will be used as a generic term encompassing all classes of thiaarenes unless otherwise specified. They have also been described as ylide-like compounds with substantial charge separated character.² Their method of preparation and properties have been the subject of some controversy in the literature.³

PRELIMINARY WORK

In early work in this area, Price^{4a,b} reported the synthesis (Eq. 1) of a compound claimed to be 1,3,4,6-tetraphenylthiabenzene (1a) by the addition



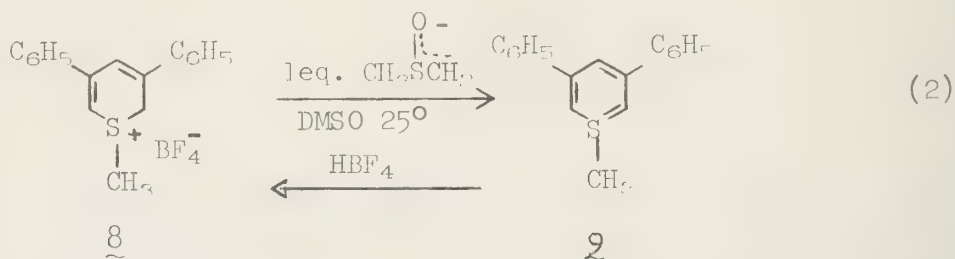
of excess phenyllithium to 2,4,6-triphenylthiopyrylium perchlorate (2). Compound 1a was reported by Price to be an amorphous violet powder obtained in approximately 30% yield. The isomeric thiopyrans 3a and 3a' were also isolated as a mixture in approximately 17% yield. Mislow³, ^{5a-c} later disputed the claim that 1a and other similar compounds reported by Price^{1,6,7a,b} and Hori^{8a-e} are true thiabenzenes. Attempts by Price⁹ to prepare the corresponding S-alkyl thiabenzenes 1b-d using Grignard reagents gave only the isomeric thiopyrans 3b-d and 3b'-d', although thiabenzenes were proposed as possible intermediates because of the fleeting appearance of purple colors after the addition of the Grignard reagents. An attempted synthesis of 1d using n-butyllithium produced similar results. Price^{6,7a} also reported the synthesis of the basic systems 4, 5, 6, and 7 as well as many substituted analogs using the same procedure



as for 1a. These compounds were all reported by Price to be highly stable amorphous powders with ^1H NMR spectra consisted solely of multiplets in the range δ 6.9-7.6 ppm. Price¹ interpreted these results as an indication of aromatic type ring current effect due to a continuous π orbital in the S-ring using the d orbitals of sulfur. Mislow³ repeated Price's synthesis of 4, 5, 6, and 7. He obtained powders as described by Price; however, he reported that the powders gave erratic microanalyses and that the ^1H and ^{13}C NMR spectra consisted of broad envelopes centered at approximately δ 7.1 ppm (^1H $W_{1/2}$ = 0.5 ppm) and δ 126 ppm (^{13}C). Mislow determined, by vapor phase osmometry in benzene, the average molecular weights of these compounds to be: 4, 968 (174 calcd.); 5, 1380 (224 calcd.); 6, 919 (224 calcd.); and 7, 831 (274 calcd.). Price^{6,7a} had obtained the following molecular weight determinations by the Rast method and cryoscopic determinations in benzene: 4, 173; 6, 300; 7, 366. Price¹ observed peaks at masses greater than the molecular ion in the mass spectra of 4 and 7 which he attributed to ion-molecule reactions within the mass spectrometer. Mislow³ concluded from the NMR and molecular weight data that the amorphous powders isolated by Price and Hori were in fact compounds of high molecular weight and undetermined structure which he termed oligomer. Mislow cited the amorphous nature, melting point data, dipole moments, and mass spectra as being consistent with this conclusion.

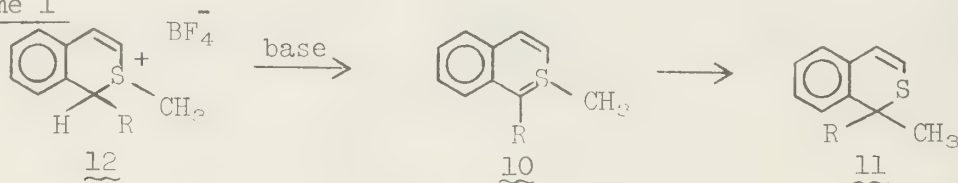
PREPARATION

Hortmann and Harris^{2,10} found that deprotonation of 1-methyl-3,5-diphenyl-2H-thiinium tetrafluoroborate (8) with one equivalent of base (Eq. 2) gave 1-methyl-3,5-diphenylthiabenzene (9) on the basis of the



^1H NMR data. Unlike Price's and Hori's compounds, 9 exhibited an AX_2 pattern upfield at δ 6.18 and 4.03 ppm (J = 1.7 Hz) which was assigned to the S-ring protons. Treatment of 9 with one equivalent of fluoboric acid resulted in the reprotonation of 9 to form 8. This agrees with Märkl's¹¹ observations concerning the acid-base behavior of phosphabenzenes. Attempts to isolate 9 yielded yellow oils and gums which appeared by ^1H NMR spectroscopy to contain about 50% 9. Hortmann and Harris² also prepared 1-phenyl-2-methyl-2-thianaphthalene (10a) and 1-(p-chlorophenyl)-2-methyl-2-thianaphthalene (10b) by the same procedure (Scheme 1). Thianaphthalenes 10a and 10b exhibited upfield doublets at δ 5.64 and 7.75

Scheme 1



- a, R = C_6H_5
 b, R = $\text{p-ClC}_6\text{H}_4$

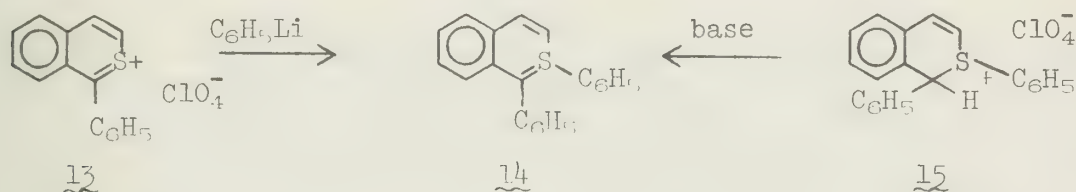
ppm ($J = 8$ Hz) and δ 5.75 and 7.05 ppm ($J = 8$ Hz), respectively.

Thianaphthalenes 10a and 10b were found to rearrange during an unspecified period of time at probe temperatures to form the isomeric 2-thio-3-chromenes, 11a and 11b (Scheme 1). This rearrangement was found to be temperature dependent and ^1H NMR spectra taken at $20-30^\circ$ showed "no significant change" from the initial spectrum after 1.5 hrs.

Treatment of 9 with a small quantity of deuterium oxide produced exchange of the 2- and 6-protons and a slower exchange of the 4-proton. This could be interpreted as evidence for greater negative charge density on the 2- and 6-carbons than on the 4-carbon although steric effects cannot be ruled out. When 8 was treated with deuterium oxide a similar, although slower, exchange was observed. Finally, it was found that treatment of 9 with excess tetradeuterioacetic acid quickly produced tetradeuterated 8. From these experiments it was concluded that the sulfonium salts and corresponding thiabenzenes are in a rapid acid-base type equilibrium.

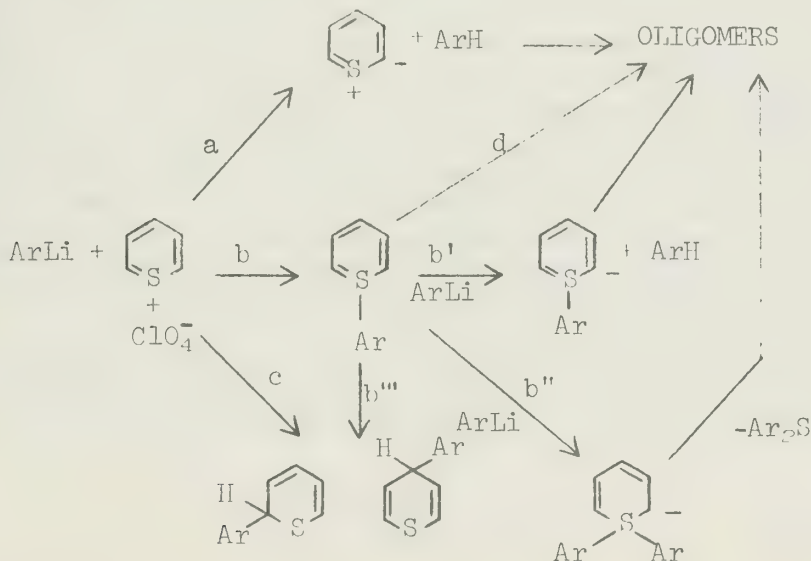
Mislow³ found that when 13 is treated with one equivalent of phenyllithium (Scheme 2) the solution turns purple and the ^1H NMR spectrum consists of an

Scheme 2



aromatic multiplet and an upfield doublet. Mislow assigned this spectrum to 1,2-diphenyl-2-thianaphthalene (14). This spectrum agrees exactly with the results obtained by deprotonation of 15 with one equivalent of base except for slight solvent effects in the ^1H NMR spectrum. This also parallels the earlier results of Hortomann and Harris for S-alkyl thiabenzenes. Upon standing, solutions of 14 gradually produced ^1H NMR spectra like those reported by Price.^{7b} Mislow³ interpreted this as decomposition of 14 to form oligomer. Mislow³ also treated several sulfonium salts with various amounts of *p*-tolyllithium and identified the volatile products. The residues were found to be very similar to Price's amorphous powders. From these results Mislow proposed Scheme 3 to explain the major products (toluene, *p*-tolylsulfide, the isomeric thiopyrans, and oligomers).

Scheme 3



BONDING

Hortmann and Harris² have proposed the Dewar model of phosphonitric halides^{1,2} (Fig. 1A) to explain their conclusions that S-alkyl thiabenzenes (Fig. 1C) are very unstable compounds with substantial ylide character (Fig. 1D). This model has also been proposed by Markl¹¹ for phosphabenzene (Fig. 1B). This bonding scheme involves the use of sp^3 hybridized orbitals of sulfur or phosphorus to form the σ bonds and accommodate the lone pair of electrons.

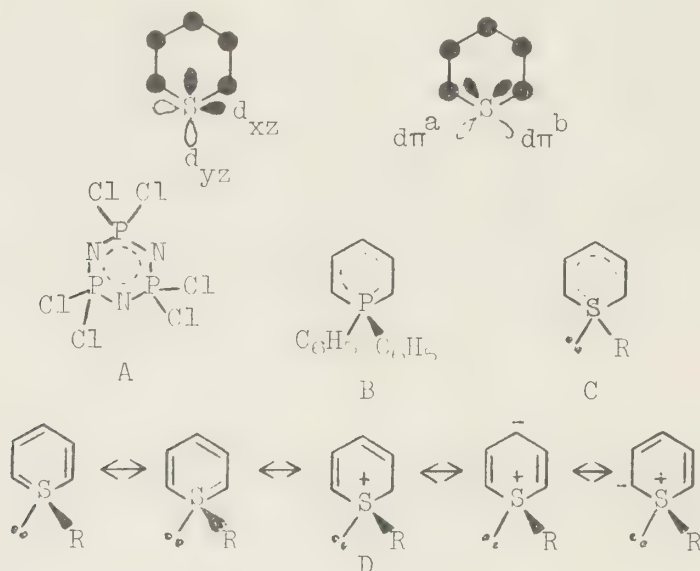


Fig. 1. Bonding of Thiabenzenes.

The d_{xz} and d_{yz} orbitals are hybridized to form two orbitals designated d_{π}^a and d_{π}^b . These orbitals can overlap with the p_z orbitals of the ring carbons or nitrogens. This produces π molecular orbitals with nodes at the sulfur or phosphorus atoms and, thus, no ring current effects are possible. The π bond of phosphonitric halides would consist of several three-centered bonds, while those of phosphabenzene and thiabenzene would have one cyclic six-centered bond. Mislow³ has indicated that the degree to which the d orbitals may participate in any π bonding and thus the degree of charge separated character is still open for discussion.

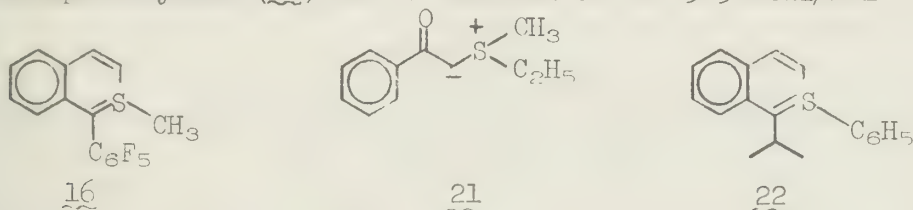
PROPERTIES

Mislow^{3,5b} has succeeded in isolating 1-pentafluorophenyl-2-methyl-2-thianaphthalene (16) as orange-red crystals from the deprotonation of the corresponding 2-thio-3-chromenium salt. It has been characterized by ^1H and ^{13}C NMR spectroscopy as well as by microanalyses, exact mass spectrometry, and molecular weight determination by vapor phase osmometry. The ^1H NMR spectrum showed the expected upfield pair of doublets, while the ^{13}C NMR spectrum exhibited a resonance, at δ 92.5 ppm (relative to TMS), which was assigned to C-3. The next resonance at higher field (δ 117.7 ppm) was assigned to C-4 by specifically decoupling the C-4 proton. Mislow^{3,5b} concluded from these results that S-aryl thiabenzenes are very similar to the S-alkyl thiabenzenes reported by Hortmann and Harris^{2,10} (i.e., they have substantial ylide or charge separated character).

Hori¹³ reported similar "ylide-like" thiabenzenes at approximately the same time as Mislow (Scheme 4). These compounds were formed by the deproto-

nation of sulfonium salts 17 and 18 with triethylamine. Thianaphthalenes 19 and 20 were isolated in high yields ($>93\%$) as orange needles. These compounds, which could be converted back to 17 and 18 with perchloric acid, exhibited the expected upfield doublet for the H-3 protons in the ^1H NMR spectra. Hori also noted that their infrared spectra indicated substantial ionic character in the carbonyl absorption for 19 (1510 cm^{-1}) and in the nitrile absorption for 20 (2142 cm^{-1}), which appear at lower frequencies than would otherwise be expected (Scheme 4). Price¹⁴ has observed similar stability properties with electron donating and withdrawing groups attached to sulfur.

Mislow has proposed that the sulfur atom in thiabenzenes is nonplanar and possesses a barrier to pyramidal inversion of approximately 40 kcal/mol based on CNDO/2 molecular orbital calculations.^{5c} This conflicts with the bonding scheme proposed by Price in which the thiabenzene has a barrier to pyramidal inversion of approximately 5 kcal/mol based on Huckel molecular orbital calculations.¹⁵ The barrier to pyramidal inversion for ethylmethylsulfoniumphenacylide (21) was determined to be 23.3 kcal/mol.¹⁶ Mislow^{3,5c}



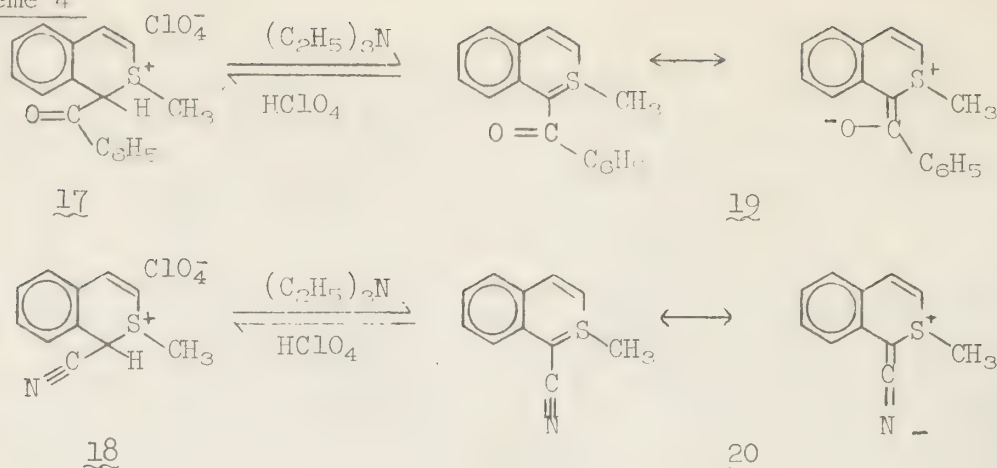
attempted to resolve this question by synthesizing a thiabenzene containing a diastereomeric group and studying the inversion by dynamic NMR. To this end, 1-isopropyl-2-phenyl-2-thianaphthalene (22) was prepared and was found to possess a pair of doublets in the ^1H NMR spectrum separated by 0.07 ppm at 37°. As the temperature was raised, rapid decomposition took place, thus only a lower limit for the barrier to pyramidal inversion (16.8 kcal/mol) could be estimated using the Gutowsky-Holm¹⁷ and Eyring¹⁸ equations.

Mislow^{3,5b} next prepared optically active 16 by deprotonation of the sulfonium salt with brucine. The thianaphthalene was found to have a circular dichroism (CD) absorption with a positive Cotton effect at the same wavelength as the visible absorption of 16. The CD absorption was found to decrease at approximately the same rate as the visible absorption decreased. The rate of pyramidal inversion was thus no faster than the rate of decomposition. From these results Mislow calculated the minimum barrier to inversion to be at least 23.7 kcal/mol.

Thermal and possible, photolytic rearrangement of thiabenzenes to their cyclic sulfide isomers (thiopyrans, etc.) was recognized by Price^{4a,9} in his early papers as well as by all other workers in the area. Mislow³ has described the reaction as a Stevens rearrangement.¹⁹ This type of rearrangement is known to occur in vinyl sulfonium ylides.²⁰ The Stevens rearrangement has been described as a four-electron [1,2] or six-electron [1,4] sigmatropic shift, although ion pair and diradical mechanisms have also been suggested.²¹ Mislow has observed CIDNP effects during rearrangement reactions. This agrees with Price's⁶ and Hori's²² earlier observations of ESR signals. These observations indicate the possibility of a radical pair mechanism. Mislow³ performed a crossover experiment in which 23a and 23d were generated together by deprotonation of the sulfonium salts 24a and 24d. The rearrangement was induced thermally by warming the mixture to room temperature. Analysis of the products indicated only 25a and 25d, with no observable crossover products (i.e., less than 3%). This agrees with a similar experiment performed by Hori.²³

Mislow²⁴ has performed a detailed kinetic study of the rearrangement of

Scheme 4



10-thiaanthracenes (Table 1). The rate of rearrangement was monitored by the

Table 1. Rates of Rearrangement in DMSO at $22 \pm 1^\circ\text{C}$.

<u>23</u>	R_1	R_2	$k \times 10^{-3}$ (sec^{-1})	No. of runs	
a	phenyl	H	13 \pm 4	10	
b	2,5-xylyl	H	8.4 \pm 1.5	6	
c	phenyl	Cl	3.5 \pm 1.5	4	
d	2,5-xylyl	Cl	1.27 \pm 0.03	3	
e	p-anisyl	H	0.8 \pm 0.09	5	
f	2,4,6-trimethoxyphenyl	H	0.61 \pm 0.04	5	
g	2,4-dimethoxyphenyl	H	0.17 \pm 0.02	4	

visible and ultraviolet spectra and was implicitly assumed to be much slower than the rate of formation by deprotonation. The rearrangements were found to be first order over at least two halflives [correlation coefficient (r) > 0.994 for each run], with no apparent dependence on the initial concentration. The rearrangement was found to be slowed by: 1) groups that could stabilize a positive charge on sulfur, and 2) a group that could stabilize a negative charge on C-2. Earlier studies by Mislow³ indicated that the rearrangement was also slower in polar solvents. This solvent effect was also observed by Hortmann.²⁵ Temperature dependent rate studies were performed by Mislow²⁴ on 23d ($\Delta H^\ddagger = 20.5$ kcal/mol, $\Delta S^\ddagger = -0.5$ eu, and $\Delta G^\ddagger = 20.65$ kcal/mol) and 23e ($\Delta H^\ddagger = 19.9$ kcal/mol, $\Delta S^\ddagger = -3.3$ eu, and $\Delta G^\ddagger = 20.87$ kcal/mol). The rates and temperatures were fitted to the Eyring¹⁸ equation using a least squares analysis. The small values of ΔS^\ddagger were cited as further verification that the rearrangement is intramolecular.

SELENABENZENES

Hori²⁶ has reported the synthesis of two selenaanthracenes which were isolated as amorphous brown powders. Mislow²⁷ has repeated Hori's work and has concluded that these compounds are also oligomers. Mislow²⁷ has also re-

ported the synthesis of the selenanaphthalene analog of 16, which was found to be much less stable than 16.

THIABENZENE-S-OXIDES

Hortmann²⁵ has prepared several thiabenzene-S-oxides. These compounds are very similar to thiabenzenes in many of their properties, but are much more stable and can be handled without special precautions such as protection from exposure to air or light. They are stable at room temperature and thus parallel Corey's²⁷ observation that acyclic sulfoxonium ylides are more thermally stable oxides to their corresponding thiabenzenes or sulfonium salts were all unsuccessful.^{10,25,29}

SUMMARY

There are currently two general methods for preparing thiabenzenes: 1) by addition of aryllithium reagents to disubstituted cyclic sulfonium salts such as 2; and 2) by deprotonation of trisubstituted cyclic sulfonium salts such as 8. The latter method is generally preferred because it gives fewer side products. Current evidence indicates that thiabenzenes are ylide-like compounds which readily decompose unless substituted with highly stabilizing groups. This ylide character is demonstrated by the upfield shift in the ¹H NMR spectrum of protons on carbons which potentially have carbanionic character and by the ease with which these protons exchange with deuterium (although steric effects may be involved). The fact that they are stabilized by properly placed electron withdrawing groups on carbon and electron donating groups on sulfur and are stabilized by polar solvents further supports this interpretation of their structure. They have been shown to be nonplanar at sulfur with a barrier to pyramidal inversion of at least ~ 20 kcal/mol. A Dewar type bonding scheme is presently favored, although the degree of d orbital participation is still unknown. They are similar to phosphabenzenes in that they both exhibit an acid-base type equilibrium with their corresponding sulfonium or phosphonium salts. Some preliminary work has been carried out on selenabenzenes, indicating that they are less stable than their sulfur analogs. Finally, several thiabenzene-S-oxides have been prepared and have been shown to be similar to thiabenzenes, although much more stable. They also represent a potential third pathway to the preparation of thiabenzenes.

REFERENCES

1. C. C. Price, J. Follweiler, H. Pirelahi, and M. Siskin, J. Org. Chem., 36, 791 (1970).
2. A. G. Hortmann, R. L. Harris, and J. A. Miles, J. Am. Chem. Soc., 96, 6119 (1974).
3. B. E. Maryanoff, J. Stackhouse, G. H. Slenker, Jr., and K. Mislow, *ibid.*,
4. (a) G. Suld and C. C. Price, *ibid.*, 83, 1770 (1961); (b) G. Suld and C. C. Price, *ibid.*, 84, 2094 (1962).
5. (a) G. H. Senkler, Jr., J. Stackhouse, B. E. Maryanoff, and K. Mislow, *ibid.*, 96, 5648 (1974); (b) J. Stackhouse, B. E. Maryanoff, G. H. Senkler, Jr., K. Mislow, *ibid.*, 96, 5650 (1974); (c) B. E. Maryanoff, B. H. Senkler, Jr., J. Stackhouse, and K. Mislow, *ibid.*, 96, 5651 (1974).
6. C. C. Price, M. Hori, T. Parasaran, and M. Polk, J. Am. Chem. Soc., 85, 2278 (1963).
7. (a) M. Polk, M. Siskin, and C. C. Price, *ibid.*, 91, 1206 (1969); (b) C. C. Price and D. H. Follweiler, J. Org. Chem., 34, 3202 (1969).
8. (a) M. Hori, T. Kataoka, and H. Shimizu, Chem. Pharm. Bull., 22, 2485 (1974); (b) M. Hori, T. Kataoka, H. Shimizu, and S. Sugai, *ibid.*, 22, 2752 (1974); (c) M. Hori, T. Kataoka, H. Hori, and S. Sugai, *ibid.*, 22, 2754 (1974); (d) M. Hori, T. Kataoka, and H. Shimizu, Chem. Lett., 1073 (1974).

9. G. Suld and C. C. Price, J. Am. Chem. Soc., 84, 2090 (1962).
10. A. G. Hortmann and R. L. Harris, J. Am. Chem. Soc., 92, 1803 (1970).
11. G. Märkl and A. Mertz, Tetrahedron Lett., 1231 (1969); G. Märkl and A. Mertz, *ibid.*, 3611 (1968); G. Märkl, Angew. Chem., 77, 1109 (1965); G. Märkl, Angew. Chem. Int. Ed. Engl., 3, 147 (1964); G. Märkl, Angew. Chem., 75, 1121 (1963); G. Märkl, 75, 669 (1963); G. Märkl, *ibid.*, 75, 168 (1963).
12. M. J. S. Dewar, E. A. Lucken, and M. A. Whitehead, J. Chem. Soc., 2423 (1960); M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N. Y., 1969, pp 430-436.
13. M. Hori, T. Kataoka, H. Shimizu, K. Narita, S. Ohno, and H. Aoki, Chem. Lett., 1101 (1974).
14. C. C. Price and H. Pirelahi, J. Org. Chem., 37, 1718 (1972).
15. C. K. Miao, M. S. Thesis, University of Pennsylvania, 1967.
16. D. Darwish and R. L. Tomilson, J. Am. Chem. Soc., 90, 5938 (1968).
17. H. S. Gutowsky and C. H. Holm, J. Chem. Phys., 25, 1228 (1956).
18. H. Eyring, Chem. Rev., 17, 65 (1935).
19. T. S. Stevens and W. E. Watts, "Selected Molecular Rearrangements", Van Nostrand, London, 1973, pp 82-83, 101-108; R. A. Booker, U. of Ill. Seminar, p 144, Spring, 1976.
20. J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, Chem. Commun., 576 (1970).
21. R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, 1971, pp 114-132.
22. M. Hori, T. Kataoka, Y. Asahi, and E. Mizuta, Chem. Pharm. Bull., 21, 1692 (1973).
23. M. Hori, T. Kataoka, and H. Shimizu, Chem. Lett., 1117 (1974).
24. F. Ogura, H. D. Hounshell, C. A. Maryanoff, W. J. Richter, and K. Mislow, J. Am. Chem. Soc., submitted for publication.
25. A. G. Hortmann, J. Am. Chem. Soc., 87, 4972 (1965).
26. M. Hori, T. Kataoka, H. Shimizu, and C. Hsü, Chem. Lett., 391 (1973); M. Hori, T. Kataoka, and C. Hsü, Chem. Pharm. Bull., 22, 15 (1974); M. Hori, T. Kataoka, H. Shimizu, C. Ashi, and E. Mizuta, *ibid.*, 22, 32 (1974).
27. J. Stackhouse, G. H. Senkler, Jr., B. E. Maryanoff, and K. Mislow, J. Am. Chem. Soc., 96, 7835 (1974).
28. E. J. Corey and M. Chaykovsky, *ibid.*, 87, 1353 (1965).
29. A. G. Hortmann and R. L. Harris, *ibid.*, 93, 2471 (1971).

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ORGANIC SEMINAR ABSTRACTS

1976-77

SEMESTER I

School of Chemical Sciences
Department of Chemistry
University of Illinois
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61801

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PRESSURE ASSISTED SYNTHESIS AND MECHANISTIC APPLICATIONS

Reported by Jim Hauske

September 9, 1976

The ability of pressure to facilitate reactions of a large variety of organic compounds is well established;^{1,2,3} yet, for preparative organic chemistry, it remains a relatively unexplored area. However, high pressure techniques, which provide reliable kinetic data, are a comparatively recent development.^{4-12,17,19,26} The effect of pressure on the rate of a reaction is defined in terms of activation volumes, ΔV^\ddagger , where $\partial \ln k / \partial p = -\Delta V^\ddagger / RT$. The activation volume is a change in the density of the surrounding solvent as reactants approach the transition state, if ΔV^\ddagger is negative, that is, a volume contraction, increased pressure will enhance reaction rates. It is useful to consider the activation volume as the sum of two terms⁷, ΔV_1^\ddagger , the structural term and ΔV_2^\ddagger , the solvation term. ΔV_1^\ddagger is the change in volume of the reacting molecules themselves when they form the transition state, while ΔV_2^\ddagger is the accompanying volume change due to interactions of the surrounding molecules (solvent) with newly formed charges in the transition state. Since pressure is uniquely suited to measure solvation changes during reaction, kinetic data obtained in this fashion would provide useful mechanistic information; particularly, for reactions which are not conducive to investigation by other, more conventional methods.⁸⁻¹² This seminar will illustrate various types of syntheses at high pressure and also will attempt to interpret high pressure kinetic data in terms of possible mechanistic alternatives.⁴⁰⁻⁴⁵

Pressure assisted syntheses of systems unreactive at 1 atmosphere under forcing conditions have been attempted by Okamoto¹³⁻¹⁶ and le Noble.^{17,18} Further, Neuman has successfully exploited high pressure techniques to conduct reactions of many radicals.^{19-25,46} Their findings indicate that in many cases these reactions proceed smoothly and afford isolable products in high yields.

Specifically, Dauben has utilized pressures in the range of 8-20 kbars at room temperature to conduct preparative (4 + 2) cycloadditions of enamines, dienamines and also furans.^{38,39} For the reaction of enamines with dienamic esters, the use of elevated pressure and mild temperature generally permits the reaction to proceed in high yield with relatively short reaction times (typically, 10 min. to 24 hr.). Apparently, these reactions become increasingly more difficult with increased substitution, as evidenced by the failure of ethyl cyclohexadienecarboxylate to react with the pyrrolidine enamine of propionaldehyde or isobutyraldehyde.³⁸ However, this may also reflect the unfavorable steric or electronic effect of an α -substituent. The reaction of dienamines with enamic esters, ene nitriles, and enones (conjugated acceptors) proceeded well under similar conditions. Again, unfavorable steric or electronic interactions of the substituent in the conjugate acceptor (dienophile) clearly impeded reaction. Further, the cycloaddition reaction was found to be sensitive to pressure, as reflected in product ratios and extents of reaction. Similar results were also reported for furans. For example, under pressure the reaction of isophorone dienamine with methyl acrylate and with acrylonitrile yielded only the Diels-Alder type adduct. These same reactions were investigated thermally and resulted in different product ratios, which were not exclusively Diels-Alder adducts.⁴⁷ Thus, pressure effects not only the course of reaction, but also product specificity.

BIBLIOGRAPHY

1. W. J. le Noble, *Prog. Phys. Org. Chem.*, 5, 207 (1967).
2. G. Kohnstam, *Prog. React. Kinet.*, 5, 335 (1970).
3. K. E. Weale, "Chemical Reactions at High Pressure", E. and F. N. Spon Ltd., London, 1967.
4. J. R. McCabe and C. A. Eckert, *Accounts Chem. Res.*, 7, 251 (1974).
5. R. C. Neuman, Jr., *Accounts Chem. Res.*, 5, 381 (1972).
6. R. Grieger, C. Chaudoir, and C. Eckert, *Ind. Eng. Chem. Fundam.*, 10, 24 (1971).
7. K. I. Lee and Y. Okamoto, *J. Org. Chem.*, 41, 1552 (1976).
8. S. D. Christian, J. Grundnes, and P. Klaboe, *J. Am. Chem. Soc.*, 97, 3864 (1975).
9. Y. Okamoto and T. Yano, *Tetrahedron Lett.*, 4285 (1971).
10. Y. Okamoto and H. Shimizu, *J. Am. Chem. Soc.*, 90, 6145 (1968).
11. W. J. le Noble and B. L. Yates, *J. Am. Chem. Soc.*, 87, 3515 (1965).
12. W. J. le Noble, B. L. Yates, and A. W. Scaplehorn, *J. Am. Chem. Soc.*, 89, 3515 (1967).
13. Y. Okamoto and Y. Shimakawa, *Tetrahedron Lett.*, 317 (1966).
14. Y. Okamoto and H. Shimizu, *Tetrahedron Lett.*, 2751 (1968).
15. Y. Okamoto, *J. Am. Chem. Soc.*, 90, 5639 (1969).
16. Y. Okamoto and Y. Shimakawa, *J. Org. Chem.*, 35, 3752 (1970).
17. W. J. le Noble and Y. Ogo, *Tetrahedron*, 26, 4119 (1970).
18. W. J. le Noble and T. Asano, *J. Am. Chem. Soc.*, 97, 1778 (1975).
19. R. C. Neuman, Jr. and E. W. Ertley, *J. Am. Chem. Soc.*, 97, 3130 (1975).
20. R. C. Neuman, Jr. and J. V. Behar, *J. Am. Chem. Soc.*, 89, 4549 (1967).
21. R. C. Neuman, Jr. and J. V. Behar, *J. Am. Chem. Soc.*, 91, 6024 (1969).
22. M. Charton, *J. Org. Chem.*, 31, 3745 (1966).
23. R. C. Neuman, Jr., G. D. Lockyer, Jr., and M. J. Amrich, *Tetrahedron Lett.*, 1221 (1972).
24. R. C. Neuman, Jr. and J. V. Behar, *J. Org. Chem.*, 36, 654 (1971).
25. R. C. Neuman, Jr. and J. V. Behar, *J. Org. Chem.*, 36, 657 (1971).
26. K. R. Brower and J. S. Chen, *J. Am. Chem. Soc.*, 87, 3396 (1965).
27. G. M. Fraser and H. M. R. Hoffman, *Chem. Commun.*, 561 (1967).
28. C. Walling and H. J. Schugar, *J. Am. Chem. Soc.*, 85, 607 (1963).
29. H. S. Golinkin, W. G. Laidlaw, and J. B. Hyne, *Can. J. Chem.*, 44, 2193 (1966).
30. C. Walling and D. T. Tanner, *J. Am. Chem. Soc.*, 85, 612 (1963).
31. S. W. Benson and J. A. Berson, *J. Am. Chem. Soc.*, 86, 259 (1964).
32. R. C. Neuman, Jr., and R. J. Bussey, *J. Am. Chem. Soc.*, 92, 2440 (1970).
33. J. W. Taylor and J. C. Martin, *J. Am. Chem. Soc.*, 88, 3650 (1966).
34. M. J. Drabicky, P. C. Myhre, C. J. Reich, and E. R. Schmittou, *J. Org. Chem.*, 41, 1472 (1976).
35. A. Streitwieser, Jr. and Alan Dafforn, *Tetrahedron Lett.*, 1435 (1976).
36. C. Brun and G. Jenner, *Tetrahedron*, 28, 3113 (1972).
37. C. Walling and D. T. Tanner, *J. Am. Chem. Soc.*, 85, 612 (1963).
38. W. G. Dauben and A. P. Kozikowski, *J. Am. Chem. Soc.*, 96, 3664 (1974).
39. W. G. Dauben and H. O. Krabbenhoft, *J. Am. Chem. Soc.*, 98, 1992 (1976).
40. R. A. Grieger and C. A. Eckert, *J. Am. Chem. Soc.*, 92, 2918 (1970).
41. R. A. Grieger and C. A. Eckert, *J. Am. Chem. Soc.*, 92, 7149 (1970).
42. K. F. Wong and C. A. Eckert, *Trans. Faraday Soc.*, 66, 2313 (1970).
43. Y. Okamoto and K. I. Lee, *J. Am. Chem. Soc.*, 97, 4015 (1975).
44. Y. Okamoto and T. Yano, *Tetrahedron Lett.*, 919 (1971).
45. W. J. le Noble, E. H. White, and P. M. Dzadzic, *J. Am. Chem. Soc.*, 98, 4020 (1976).
46. N. H. Nodelman, University of Illinois, Organic Chemistry Seminar Abstracts, p. 158 (1970-1971).
47. H. Nozaki, T. Yamaguti, S. Veda and K. Kondo, *Tetrahedron*, 24, 1445 (1968).

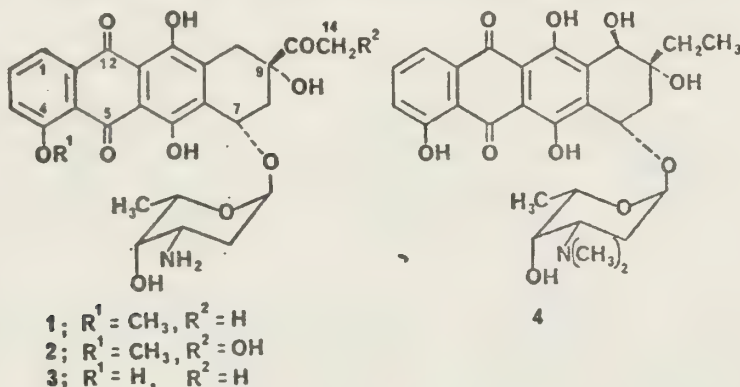
THE SYNTHESIS OF DAUNOMYCIN, ADRIAMYCIN, AND RELATED ANTHRACYCLINE COMPOUNDS

Reported by Gene E. Keyser

September 13, 1976

The antitumor antibiotic daunomycin (**1**) has been proven clinically effective as a powerful inducer of remissions in acute leukemias;¹ adriamycin (**2**) has also shown clinical utility against a variety of human cancers.² Both are metabolites of *Streptomyces peucetius*,^{3,4} the latter being generated on treatment of the parent culture with N-nitroso-N-methyl urethane.⁵ Carminomycin I (**3**) has been isolated from *Streptosporangium* sp.⁶ and *Actinomadura carminata* sp. nov.⁷ and shows promise of effectiveness as an anticancer agent, accompanied by reduced cardiotoxicity.⁸ The activity demonstrated by these compounds has aroused considerable interest in total syntheses competitive with their biosynthetic production.

The anthracyclines **1**,³ **2**,⁴ and **3**⁶ contain the same tetrahydro-5,12-naphthacenedione ring system and a related amino trideoxyhexose as does rhodomycin B (**4**).⁹ From present data, the configurations about the carbon

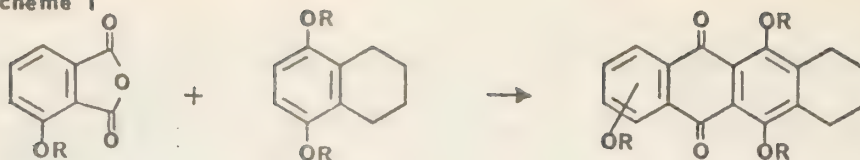


skeleton and the substitution pattern appear necessary for activity,^{10a,11} although the 9-hydroxy-9-carboxylate derivative and its methyl ester^{10a} and the 4-desmethoxy derivative^{10b} are active. The aglycone portion of **1**, daunomycinone, has recently been shown to be derived from a propionate "starter" and nine successive malonate condensations with loss of the terminal carboxyl.¹²

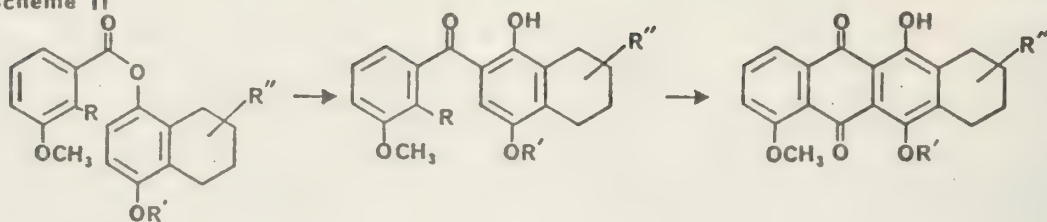
The emphasis of this review will center upon synthesis of the anthracyclinone ring system of **1**, **2**, and **3**. Prior to description of actual syntheses, discussion of the synthetic strategy currently being employed, together with some postulated methods, is in order. The more traditional procedure for formation of the tetracyclic system is the Friedel-Crafts acylation of tetrahydronaphthalene diols or protected diols with substituted phthalic anhydrides^{13,14} and phthalic acids¹⁵ (Scheme I). This method is particularly useful in cases when either reactant is symmetrical, so as to eliminate the formation of regioisomers. Conditions vary over a wide range, but the Lewis acids used generally present formidable dangers for functionality in the D ring.

A two-step modification of the Friedel-Crafts procedure employs a Fries rearrangement of a phthalic acid ester, followed by acid catalysed ring closure to give the quinone moiety (Scheme II). Again, caution must be used in prior functionalization. Not only is the problem of regioisomerism present, but also, deactivation of the diol nucleus may preclude rearrange-

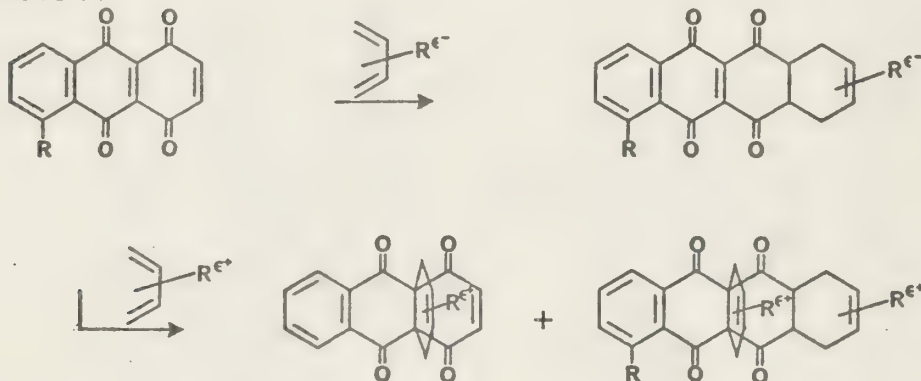
Scheme I



Scheme II



Scheme III



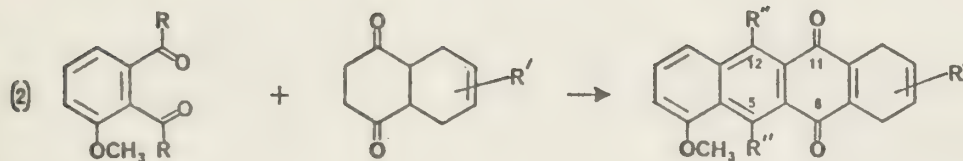
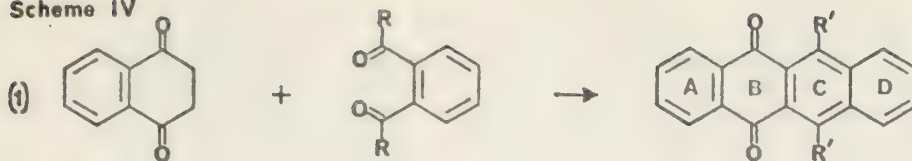
ment.¹⁶ The two methods of Fries rearrangements, photochemical and Lewis acid catalysed, differ in their susceptibility to substituent effects.^{17,18}

Another approach to the naphthacenedione system is the Diels-Alder reaction utilizing quinizarinquinone as the dienophile¹⁹ (Scheme III). This takes advantage of the fact that electron deficient and unsubstituted dienes react preferentially at the external double bond to give 6,11-dihydroxy-naphthacenediones, while electron rich dienes react at the internal double bond or both to give propellanes.²⁰ For example, butadiene and 2-acetoxybutadiene react primarily at the external double bond to give linear adducts.^{20,21}

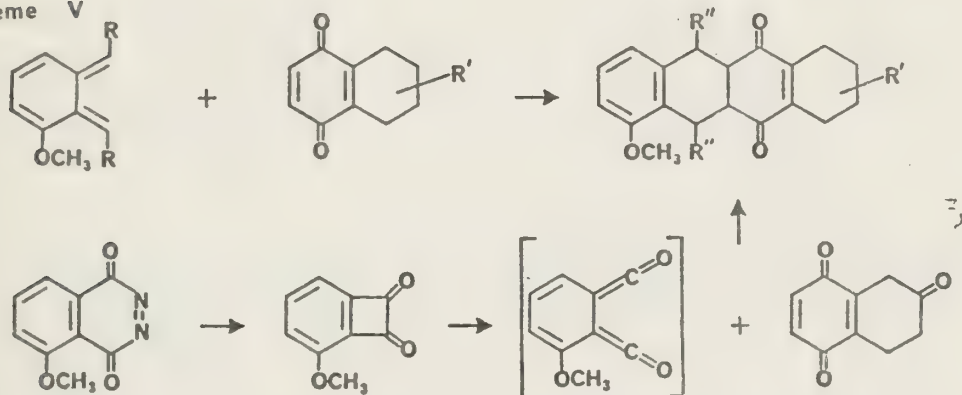
A double aldol condensation of dihydro-naphthaquinone with ortho dialdehydes has been used to prepare the parent ring system, unsubstituted at the 6 and 11 positions.²² Suitable modification of the oxidation level of the ortho dialdehyde, serving as the D ring precursor, might provide 6,11-substitution of the product (Scheme IV; eq. 1). An interesting application of this reaction appeared recently²³ using the ortho dialdehyde as the A ring precursor and a 1,4-diketone derived from the Diels-Alder adduct of dienes with benzoquinone (eq. 2).

Alternate approaches to the substituted tetracyclic system, as yet unreported, might be as shown in Scheme V, based on work by Sammes and others.²⁴ Complete functionalization of both halves might be possible in the example given, allowing for a mixture of isomers. Further possible Diels-Alder combinations, each having their own virtues and potential hazards, are shown in Scheme VI.^{25,26}

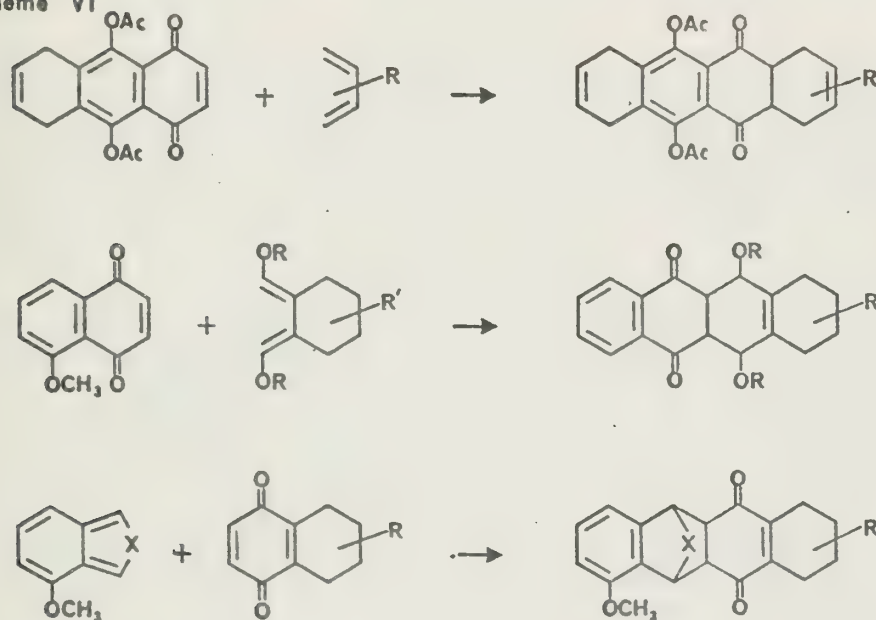
Scheme IV



Scheme V

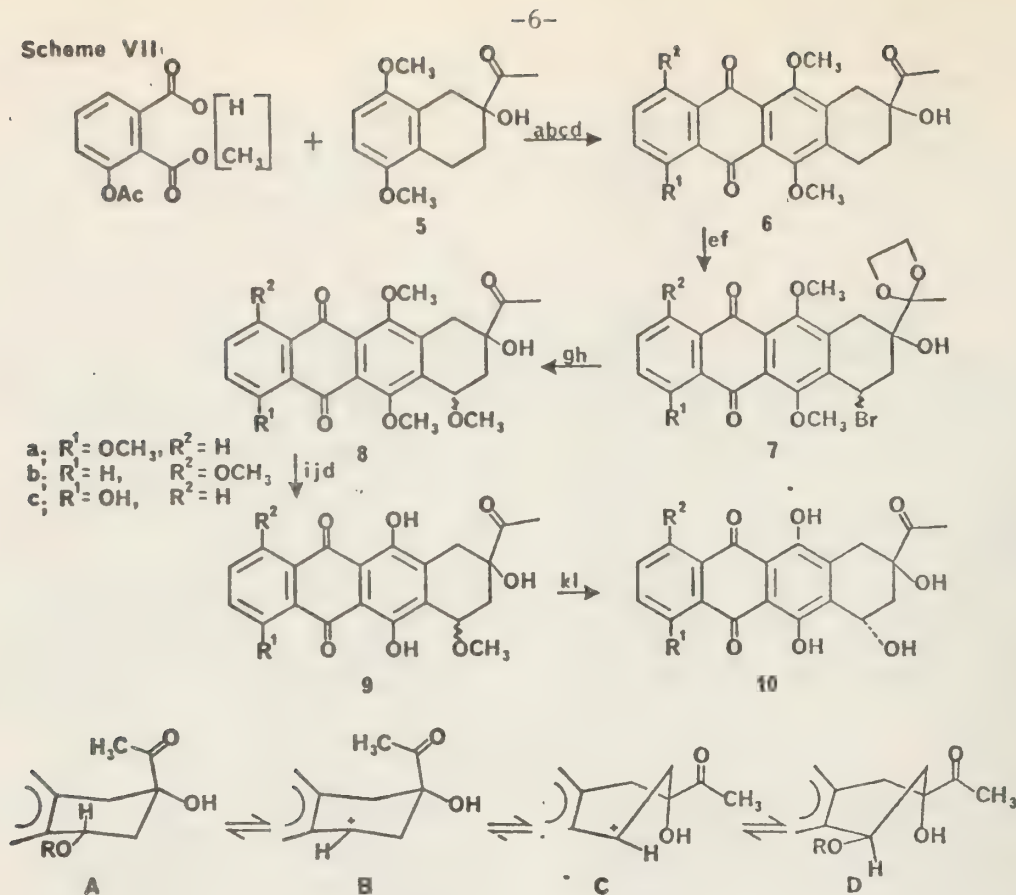


Scheme VI



With the exception of the photo-Fries reaction, admittedly a weighted example, the available methods must use symmetrical precursors or suffer the fate of separation of regioisomers at some point. Although the Lewis acid-catalysed Fries rearrangement showed promise of regioselectivity in model systems,¹⁷ it too suffered in the final test. Some methods of the Friedel-Crafts approach, the Diels-Alder cycloadditions, and the double

Scheme VII.

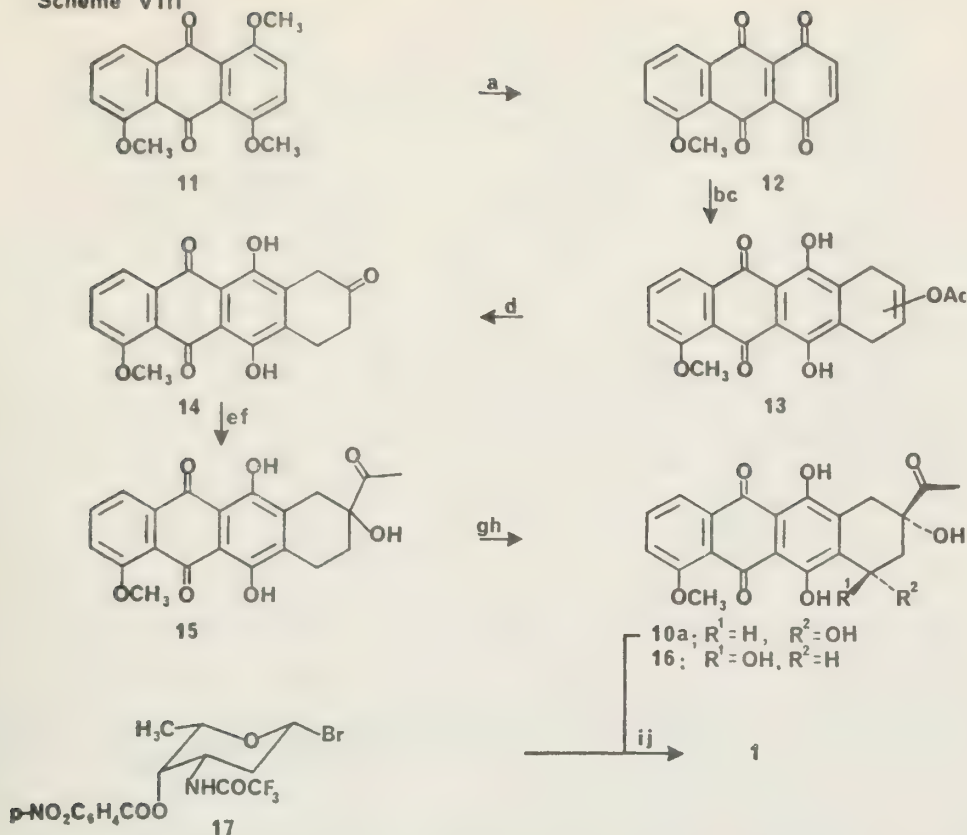


a, $(\text{CF}_3\text{CO})_2\text{O}$; b, NaOH ; c, HF ; d, $(\text{CH}_3)_2\text{SO}_4$, K_2CO_3 ; e, ethylene glycol, $p\text{-TsOH}$; f, NBS ; g, MeOH ; h, H_2O^+ ; i, AlCl_3 ; j, $\text{Pb}(\text{OAc})_4$; k, TFA ; l, NH_4OH .

aldol condensation enjoy the advantage of simultaneous formation of two bonds which compensates for the disadvantage of isomer production. The Diels-Alder methods also allow greater substitution of the reactants, although due regard for electronic effects must be taken. The use of two two-bond forming reactions in Scheme IV and the convergent Scheme V have not yet been realized, but these sequences do present interesting possibilities.

The work of Wong *et al.*^{27,28} represented the first total synthesis of the aglycone daunoside (11a), and as such, deserves mention irrespective of the strategy used. The dimethoxy tetralin 5 served as the CD portion in the CD \rightarrow ABCD annelation sequence, itself available in ca. 25% yield from 2,5-dimethoxy benzaldehyde. Friedel-Crafts acylation of (\pm) 5 (Scheme VII) with a mixture of 3-acetoxypthalic acid monomethyl esters yielded a mixture of diaryl ketones, which upon saponification, cyclization, and methylation gave the mixture of quinones 6a and 6b. Functionalization of the C-7 position was accomplished by protection of the acetyl side-chain and bromination with N-bromosuccinimide. Methanolysis of the unstable bromides (7) proceeded with deketalization to give two epimeric mixtures, 8a and 8b, in a ratio of 1:1. After separation, epimeric 8a was converted to daunoside (10a) by aluminum chloride demethylation, oxidation to the unstable diquinone, remethylation (presumably with reduction), and acetolysis followed by hydrolysis. Similarly, 8b was converted to isodaunoside (10b).

Scheme VIII

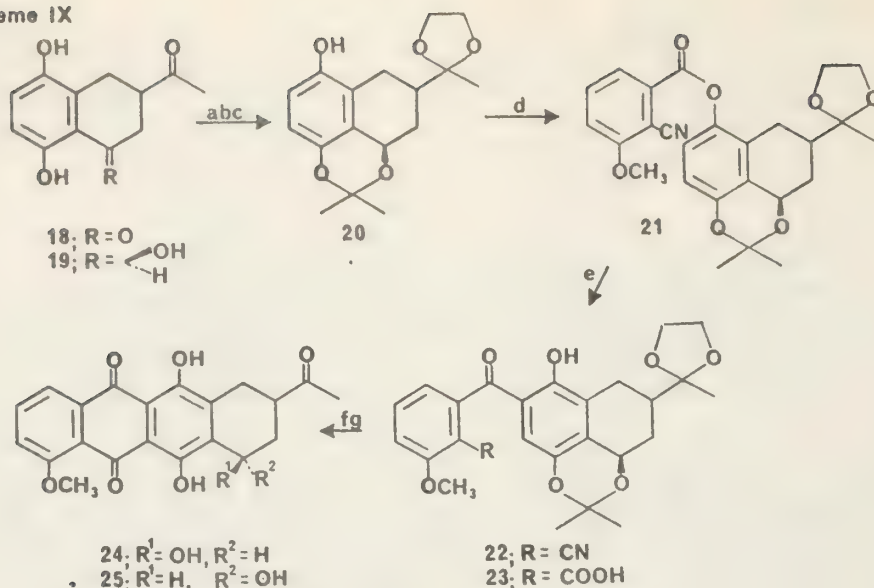


a, Ag(II)O; b, 2-acetoxybutadiene; c, AcO⁻Na⁺, AcOH; d, EtOH, HCl; e, HCCMgBr; f, HgO, H₂SO₄; g, Br₂, hv; h, H₂O on silica gel; i, Hg(CN)₂, HgBr₂; j, NaOH, THF.

An explanation offered by Wong²⁷ for the kinetic stereoselectivity of solvolysis reactions at C-7 compares conformers β and ζ , which are similar energetically. In β , nucleophiles will approach mainly from the α -side, to give Λ , due to the steric effect of the axial C-9 acetyl group; while in ζ , approach of the nucleophile from the β -side, to give Δ , is slightly favored.

Kende's total syntheses^{18,20} make varying use of cycloaddition reactions. His most recent²⁰ synthesis of daunomycinone (Scheme VIII) utilizes the reactivity of quinizarinquinone outlined in Scheme III.¹⁹ The dienophile $\underline{12}$ is prepared²⁹ from $\underline{11}^{20a}$ in 98% yield and combined with 2-acetoxybutadiene to give a 1:1 isomeric mixture of products, derived from addition to the external bond, which are tautomerized to $\underline{13}$. Hydrolysis of the enol acetate function in acidic ethanol afforded a mixture of the key intermediate $\underline{14}$ and its regioisomer in 59% overall yield; the isomers were separated by recrystallization. Introduction of the acetyl side chain was accomplished by use of ethynylmagnesium bromide followed by hydrolysis to give racemic $\underline{15}$. Photobromination (Br₂, CCl₄, hv) at the C-7 position and hydrolysis of the products on moist silica gave (±) daunomycinone ($\underline{10a}$) and (±) epidaunomycinone ($\underline{16}$). Compound $\underline{16}$ was epimerized under thermodynamic control by dissolution in trifluoroacetic acid and aqueous workup; the yield of (±) $\underline{10a}$ was ca. 50% from $\underline{15}$. The anthracycline (±) carminomycinone ($\underline{10c}$) could be obtained in nearly quantitative yield by aluminum chloride demethylation of $\underline{10a}$. This sequence makes available 3g of daunomycinone from 100g of $\underline{12}$. Conversion to (±) daunomycin, chemically identical to the natural material, could have been realized by the method of Henry *et al.*³⁰ Daunomycinone is treated with

Scheme IX



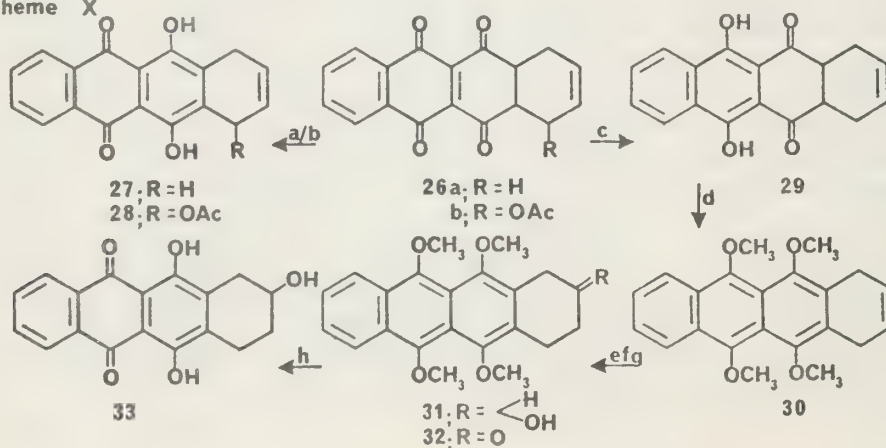
a, ethylene glycol, p-TsOH; b, NaBH₄; c, 2,2-dimethoxypropane; d, pyridine, p-TsCl, 2-cyano-3-methoxybenzoic acid; e, hv; f, NaOH; g, HF, then Na₂CO₃.

bromo-sugar 17 in the presence of mercuric cyanide and mercuric bromide. Removal of the acyl protecting groups from the sugar portion afforded 1 in ca. 50% yield from daunomycinone.

Kende's first route to daunomycinone was apparently stopped short of introducing the hydroxy function at C-9. The CD precursor 18 was prepared from its known dimethyl ether.²⁷ Protection of the acetyl side chain (Scheme IX) and reduction of the remaining ketone function gave alcohol 19, which was protected as its acetonide (20). Acylation by the Brewster-Ciotti method³¹ yielded the ester 21. Irradiation of 21 provided the diaryl ketone 22, from which acid 23 was obtained by basic hydrolysis. Cyclization and deprotection were accomplished by treatment with liquid hydrofluoric acid at room temperature, giving anthracycline 25, and not 24; thus, inversion about C-7 must have occurred concomitantly with cyclization or during workup.

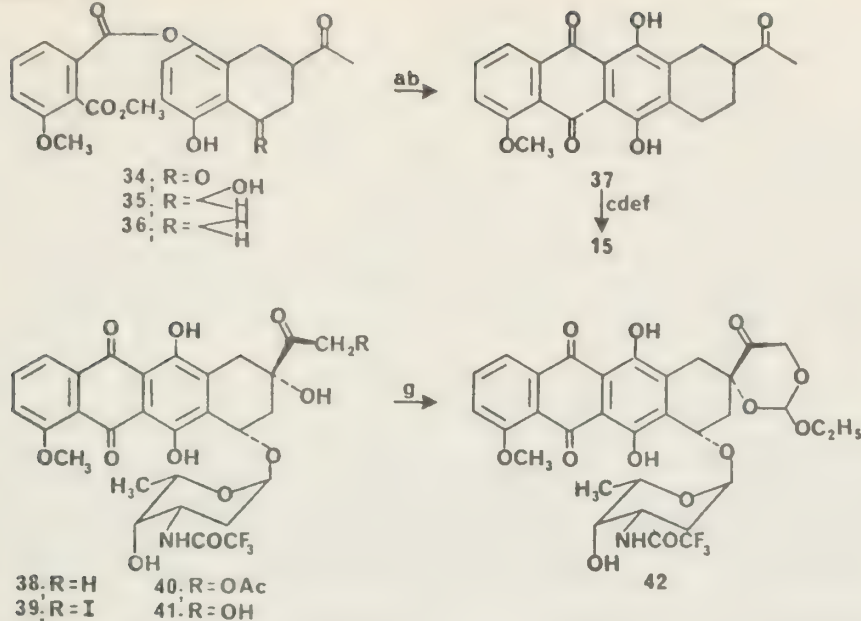
Henry and his coworkers at Stanford Research Institute have studied the synthesis,^{21,30,32} interconversions,³³ modifications,¹¹ and activity^{10,11} of these antineoplastic agents. The major feature of their efforts has been the application of the Diels-Alder approach to the synthesis of the ring

Scheme X



a, xylene, reflux; b, CH₃CN with molecular sieves; c, Zn-AcOH; d, (CH₃)₂SO₄, BaSO₄; e, B₂H₆; f, H₂O₂; g, DMSO, DCC, TFA, pyridine; h, AlCl₃.

Scheme XI



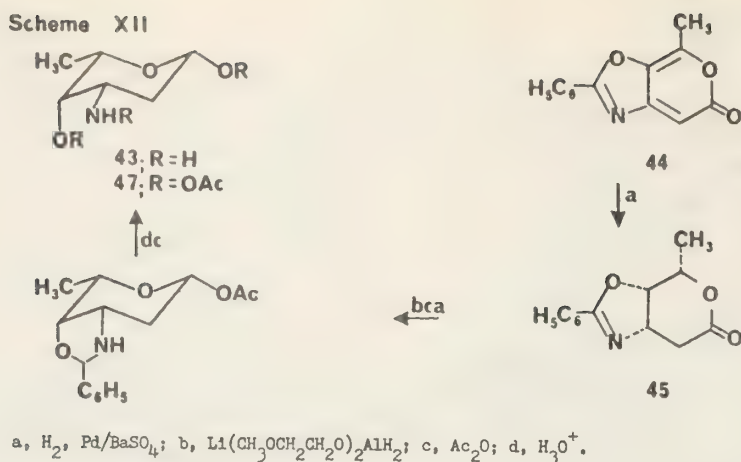
a, H_2 , Pd/C; b, BF_3 etherate; c, Ac_2O , p-TsOH; d, m-CPBA; e, NaOH; f, H_3O^+ ; g, $(EtO)_3CH$, p-TsOH.

system.²¹ The tetraketone 26a was easily converted to 27 (Scheme X), but the more sensitive 26b was tautomerized to 28 only with difficulty because of its tendency to eliminate acetic acid. Zinc-acetic acid treatment of 26a gave 29, which could be permethylated to give 30. Treatment of 30 with reagents for the conversion of alkenes to ketones did not yield the ketonic product 32 expected. Successful conversion of olefin 30 to 32, however, could be achieved by hydroboration-oxidation to alcohol 31, followed by Pfitzner-Moffatt oxidation. Unfortunately, 32 proved to be unstable under a variety of conditions, and as such, an unsuitable intermediate. Compound 31 was demethylated to dihydroxy quinone 33, but no use of this compound was reported.

Henry³³ has shown the importance of ketone 14, which can also be derived from daunomycin,³³ in production of both daunomycinone and adriamycinone. Treatment of the tetrahydropyranyl cyanohydrin of 14 with an excess of methyl magnesium iodide followed by deprotection gave 15. Benzylic bromination of 15 (Br_2 , CCl_4 , AIBN) followed by buffered trifluoroacetylation and finally methanolysis gave daunomycinone (10a). Functionalization of the C-14 position was accomplished by bromination in chloroform followed by base hydrolysis. An alternative which would use the methoxyvinyl lithium synthon for introduction of the acetyl or hydroxy-acetyl side chain has been proposed recently,³⁴ placing an even greater interest on 15 as a key synthetic intermediate.

Investigations by Sih^{16,17} employ the Lewis acid catalysed Fries rearrangement for AB ring annelation to give an intermediate tetrahydro-5,12-naphthacenequinone. Regiospecific acylation of hydroquinone 18 with 2-carbomethoxy-3-methoxybenzoic acid gave the phthalate 34 (Scheme XI). Treatment of 34 with boron trifluoride-etherate gave only low yields of tetracyclic products, as did the alcohol 35, its phenolic methyl ether and phenolic isobutyl carbonate, emphasizing the susceptibility of the reaction to deactivating substitution. Acidic hydrogenolysis of 34 gave the tetralin 36, which on treatment with boron trifluoride-etherate gave a mixture of the tetracyclic

Scheme XII



37 and its regioisomer. Conversion of 37 to the C-9 hydroxy compound 15 was achieved via enol acetylation, epoxidation, and alkaline and acid hydrolyses, respectively. Combined with Kende's utilization of 15 and work by Henry, this route allows access to the three anthracyclones of interest.

Conversion of daunomycin to adriamycin and the use of the key intermediate 15 to synthesize adriamycin³³ represent valuable sources of the latter compound, which has shown greater clinical utility. Arcomone, a pioneer⁵ in the biosynthetic production of both 1 and 2, has achieved their interconversion via the following method.³⁵ The N-trifluoroacetyl daunomycin (38) is converted to the C-14 iodide 39 by the action of iodine and calcium oxide. Treatment of 39 with anhydrous sodium acetate in acetone yields the α-acetoxo ketone 40, which is converted to N-trifluoroacetyl adriamycin (41) with bicarbonate in aqueous ethanol. Masking of the dihydroxy acetone side chain was accomplished by formation of the ortho ester 42 from 41. Subsequent basic hydrolysis of the N-acyl function followed by acid hydrolysis of the orthoformate furnished adriamycin in an overall yield of 35% from 1.

Synthesis of daunosamine (43), the sugar portion of 1, 2, and 3, has been realized by conventional transformations yielding the natural L-isomer.³⁶ However, Wong³⁷ has strayed from the normal carbohydrate interconversion by demonstrating the utility of the oxazolo-α-pyrone 44 as a precursor for 43. Hydrogenation gave the all-cis 45. Reduction of the carbonyl, acetylation, and further hydrogenation gave the protected sugar 46. Removal of the benzylidene group by treatment with acid and acetylation of the amino alcohol gave the triacetyl derivative of dl-daunosamine (47).

Continuing efforts to synthesize daunomycin, adriamycin, and carminomycin are extant. Following these efforts will be most interesting in light of the strategic alternatives available.

BIBLIOGRAPHY

1. C. Tan, H. Tasaka, K. Yu, M. L. Murphy, and D. A. Karnofsky, *Cancer*, **20**, 333 (1967); Cl. Jacquillat *et al.*, *Arzneim. Forsch.*, **17**, 955 (1967).
2. R. H. Blum and S. K. Carter, *Ann. Intern. Med.*, **80**, 249 (1974).
3. F. Arcomone *et al.*, *J. Am. Chem. Soc.*, **86**, 5334, 5335 (1964).
4. F. Arcomone, G. Franceschi, S. Penco, *Tetrahedron Lett.*, 1007 (1969).
5. F. Arcomone *et al.*, *Biotech. and Bioeng.*, **11**, 1101 (1969).
6. M. Wani, H. L. Taylor, M. E. Wall, A. T. McPhail, and K. D. Onan, *J. Am. Chem. Soc.*, **97**, 5955 (1975).

7. G. R. Pettit et al., ibid., 97, 7387 (1975).
8. M. G. Braznikova, V. B. Zbarsky, V. I. Ponomarenko, and N. P. Potapova, J. Antibiot., 27, 254 (1974).
9. H. Brockman, Fortschr. Chem. Org. Naturstoffe, 21, 121 (1963).
10. (a) D. W. Henry, G. Tong, W. W. Lee, D. R. Black, J. Med. Chem., 19, 396 (1976);
(b) Patented (1975) by Farmitalia.
11. D. W. Henry, E. M. Acton, and K. Yamamoto, ibid., 15, 872 (1972).
12. H. W. Whitlock, M. L. Casey, and R. C. Paulick, J. Am. Chem. Soc., 98, 3370 (1976).
13. Z. Horii, H. Hakusui, T. Momose, and E. Yoshino, Chem. Pharm. Bull. 16, 1251 (1968).
14. J. Finkelstein and J. A. Romano, J. Med. Chem., 13, 568 (1970).
15. H. Brockman, Tetrahedron Lett., 45 (1966).
16. C. J. Sih, S. Trenbeath, and D. G. Miller, ibid., in press, 1976.
17. C. J. Sih, S. Trenbeath, and D. G. Miller, ibid., 1637 (1976).
18. A. S. Kende et al., Syn. Comm., 3, 387 (1973); J. Am. Chem. Soc., 97, 4425 (1975).
19. H. H. Inhoffen, H. Muxfeldt, V. Koppe, and J. Trosien, Chem. Ber., 90, 1448 (1957).
20. A. S. Kende, Y. Tsay, and J. E. Mills, J. Am. Chem. Soc., 98, 1967 (1976).
21. D. W. Henry, W. W. Lee, A. P. Martinez, and T. H. Smith, J. Org. Chem., 41, 2296 (1976).
22. Y. Lepage and A. Verine, Compt. Rend. Acad. Sc. C, 274, 1534 (1972).
23. W. Lange, Z Naturforsch B, 31, 398 (1976).
24. P. G. Sammes, Tetrahedron, 32, 405 (1976).
25. F. Farina and J. C. Vega, Tetrahedron Lett., 1655 (1972).
26. A. S. Kende, A. C. S. Great Lakes Regional Meeting, May, 1976.
27. C. M. Wong, D. Popien, R. Schwenk, and J. Raa, Can. J. Chem., 49, 2712 (1971).
28. C. M. Wong, D. Popien, R. Schewnk, and T. Ho, ibid., 51, 466 (1973).
29. C. D. Snyder and H. Rapoport, J. Am. Chem. Soc., 94, 227 (1973).
30. E. M. Acton, A. N. Fujiwara, and D. W. Henry, J. Med. Chem., 17, 659 (1974).
31. J. H. Brewster and C. J. Ciotti, Jr., J. Am. Chem. Soc., 77, 6214 (1955).
32. J. P. Marsh, R. H. Iwamoto, and L. Goodman, Chem. Comm., 589 (1968).
33. T. H. Smith, A. N. Fujiwara, D. W. Henry, and W. W. Lee, J. Am. Chem. Soc., 98, 1969 (1976).
34. J. E. Baldwin, O. W. Lever, Jr., N. R. Tzodikov, J. Org. Chem., 41, 2312 (1976).
35. F. Arcomone, W. Barbieri, G. Franceschi, and S. Penco, Chim. Ind., 51, 834 (1969).
36. J. P. Marsh, C. W. Mosher, E. M. Acton, and L. Goodman, Chem. Comm., 973 (1967); D. Horton, Carbohy. Res., 44, 227 (1975); F. Arcomone, ibid., 14, 65 (1970); 46, 3 (1976).
37. C. M. Wong, T. Ho, and W. P. Nienczura, Can. J. Chem., 53, 3144 (1975).

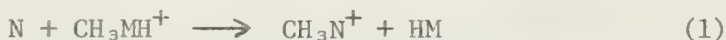
NUCLEOPHILIC GAS PHASE SUBSTITUTION REACTIONS

Reported by Bruce Allison

September 20, 1976

The recent interest in gas phase ion-molecule reactions has been spurred by a desire to investigate the kinetics, mechanism, and thermodynamics of a variety of common organic reactions in the absence of intrinsic solvation effects.¹ These reactions have been studied by ion cyclotron resonance spectrometry,² high pressure mass spectrometry,³ and flowing afterglow spectrometry.⁴

S_N2 Type Reactions. Bohme has shown that many nucleophiles react with methyl chloride displacing chloride as the primary reaction channel.⁵ The intrinsic nucleophilicities of the anions NH₂⁻, OH⁻, and F⁻ are equal and do not correlate with their gas phase basicities.^{6,7} Beauchamp has investigated reactions of the general type



where N = N₂,⁸ CO,⁸ HCl,⁹ H₂O,⁹ and Xe;¹⁰ and M = F,^{8,10} and Cl.⁹ Ammonia and methylamine have also been shown to react as nucleophiles with azomethane.¹¹ These reactions proceed providing two criteria are met: (1) the reaction is exothermic, and (2) proton transfer from the protonated substrate to the nucleophile is endothermic.⁹

Brauman has reported that the reaction of chloride ions with cis and trans substituted 4-bromocyclohexanols proceeds with inversion of stereochemistry,¹² that the reactions are first order in nucleophile and substrate,¹³ and that the rate ratio for attack of nucleophile on methyl chloride and methyl bromide is inverted on changing the nucleophile from fluoride to methyl sulfide, providing support for the assertion that Pearson's hard-soft acid-base principle¹⁴ is not solely a matter of solvation.¹³

Dougherty and Roberts have observed halide association ions (eq. 2) and propose that these ions are directly related to the S_N2 transition state of solution chemistry,¹⁵ that their stabilities reflect the stabilities of S_N2 transition states in the absence of solvents,¹⁶ that solvent controls nucleophilic reactivity,¹⁶ and that structural effects in the substrate are solvent controlled.¹⁷

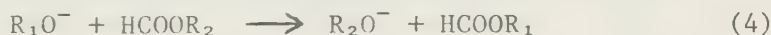


DePuy and Shapiro¹⁸ have studied the reactions of nucleophiles with ethylene oxide and propylene oxide and found addition reactions analogous to nucleophilic substitution reactions. Bohme¹⁹ has observed nucleophilic displacement of hydrogen in the reaction of D⁻ with SiH₄.

Substitution Reactions at Carbonyl Carbon. Brauman²⁰ has observed reactions of the type



providing support for a proposed tetrahedral intermediate. Riveros²¹ has reported a gas phase analog of the transesterification reaction (eq. 4) which occurs only when R₁ is less bulky than R₂.



A tetrahedral intermediate capable of assuming a six membered ring conformation has been proposed in the reaction of F⁻ and OH⁻ with alkyl for-

mates.²² Bowie²³ has also observed 1:1 adducts in the reactions of acetate anions with carboxylic anhydrides.

Nucleophilic Aromatic Substitution Reactions. Riveros²⁴ has shown that attack by alkoxide ions of fluorosubstituted benzenes gives rise to a substituted phenoxide ion.

BIBLIOGRAPHY

1. E. M. Arnett, *Acc. Chem. Res.*, 6, 404 (1973).
2. (a) J. L. Beauchamp, *Annu. Rev. Phys. Chem.* 22, 527 (1971); (b) J. L. Beauchamp, M. C. Caserio, and T. B. McMahon, *J. Am. Chem. Soc.*, 96, 6243 (1974); (c) J. I. Brauman, J. M. Riveros, and K. L. Blair, *ibid.*, 93, 3914 (1971).
3. K. Hiraoka, E. P. Grimsrud, and P. Kebarle, *J. Am. Chem. Soc.*, 96, 3359 (1974).
4. (a) N. D. Twiddy, *Contemp. Phys.*, 15, 427 (1974); (b) D. K. Bohme and L. B. Young, *J. Am. Chem. Soc.*, 92, 3301 (1970); (c) D. K. Bohme, E. Lee Ruff, and L. B. Young, *ibid.*, 94, 5153 (1972).
5. D. K. Bohme and L. B. Young, *J. Am. Chem. Soc.*, 92, 7354 (1970).
6. L. B. Young, L. Lee Ruff, and D. K. Bohme, *J. Chem. Soc., Chem. Commun.*, 35 (1973).
7. D. K. Bohme, G. I. Mackay, and J. D. Payzant, *J. Am. Chem. Soc.*, 96, 4027 (1974).
8. D. Holtz and J. L. Beauchamp, *Nature, Phys. Sci.*, 231, 204 (1971).
9. D. Holtz, J. L. Beauchamp, and S. D. Woodgate, *J. Am. Chem. Soc.*, 92, 7484 (1970).
10. D. Holtz and J. L. Beauchamp, *Science*, 173, 1237 (1971).
11. M. S. Foster and J. L. Beauchamp, *J. Am. Chem. Soc.*, 94, 2425 (1972).
12. C. A. Lieder and J. I. Brauman, *J. Am. Chem. Soc.*, 96, 4028 (1974).
13. J. I. Brauman, W. N. Olmstead, and C. A. Lieder, *J. Am. Chem. Soc.*, 96, 4030 (1974).
14. R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, 90, 319 (1968).
15. R. C. Dougherty, J. Dalton, and J. D. Roberts, *Org. Mass Spectrom.*, 8, 77 (1974).
16. R. C. Dougherty and J. D. Roberts, *Org. Mass Spectrom.*, 8, 81 (1974).
17. R. C. Dougherty, *Org. Mass Spectrom.*, 8, 85 (1974).
18. V. M. Bierbaum, C. H. DePuy, R. H. Shapiro, and J. H. Stewart, *J. Am. Chem. Soc.*, 98, 4229 (1976).
19. J. D. Payzant, K. Tanaka, L. D. Betowski, and D. K. Bohme, *J. Am. Chem. Soc.*, 98, 894 (1976).
20. O. I. Asubiojo, L. K. Blair, and J. I. Brauman, *J. Am. Chem. Soc.*, 97, 6685 (1975).
21. L. K. Blair, P. C. Isolani, and J. M. Riveros, *J. Am. Chem. Soc.*, 95, 1057 (1973).
22. J. G. Faigle, P. C. Isolani, and J. M. Riveros, *J. Am. Chem. Soc.*, 98, 2049 (1976).
23. (a) J. H. Bowie, *Aust. J. Chem.*, 28, 559 (1975); (b) J. C. Wilson and J. H. Bowie, *Aust. J. Chem.*, 28, 1993 (1975); (c) J. H. Bowie and B. D. Williams, *Int. J. Mass Spectrom., Ion Phys.*, 17, 395 (1975); (d) J. H. Bowie and B. D. Williams, *Org. Mass Spectrom.*, 10, 141 (1975).
24. S. M. J. Briscese and J. M. Riveros, *J. Am. Chem. Soc.*, 97, 230 (1975).

REARRANGEMENTS OF CAMPHANES AND RELATED COMPOUNDS
FROM A SUPERACID PERSPECTIVE

Reported by Reginald A. Booker

October 4, 1976

Organic molecular rearrangements are known to occur by a number of mechanisms, but one particularly important class involves carbocations with the actual molecular rearrangement taking place in the carbocation intermediate. One such example is camphene, which has the possibility of competitive cationic rearrangements.¹ (See Figure 1.)

The first example of a postulated carbocation rearrangement was by Meerwein and Van Emster², whose generality of the Meerwein postulate was not confirmed until the subsequent work of Whitmore³ and Ingold.⁴ Extensive work^{9,10,11} in this area has led to the conclusion that no less than three competitive cationic racemization pathways are involved: (1) an endo 3,2-methyl shift; (2) an endo 6,2-hydride shift; (3) an exo 3,2-methyl shift (Figure 2).

The camphene hydro cation is easily prepared^{13,14} from isoborneol, camphene, or tricyclene in any of several superacid solvents. Degenerate rearrangement rates are derived from NMR line-broadening data.^{1,14} Knowing the absolute rate or activation barrier, ΔG^\ddagger , of the rearrangement process is of importance for full understanding of the mechanism of the reaction, and this rate dictates the choice of experimental conditions used in carrying out these reactions.¹

Figure 1

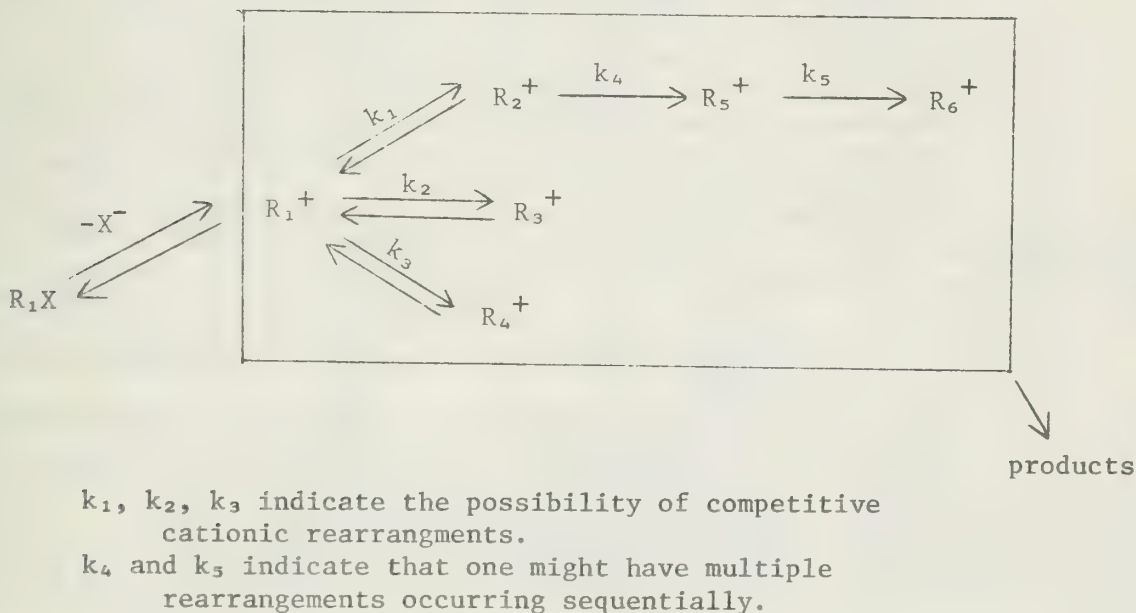
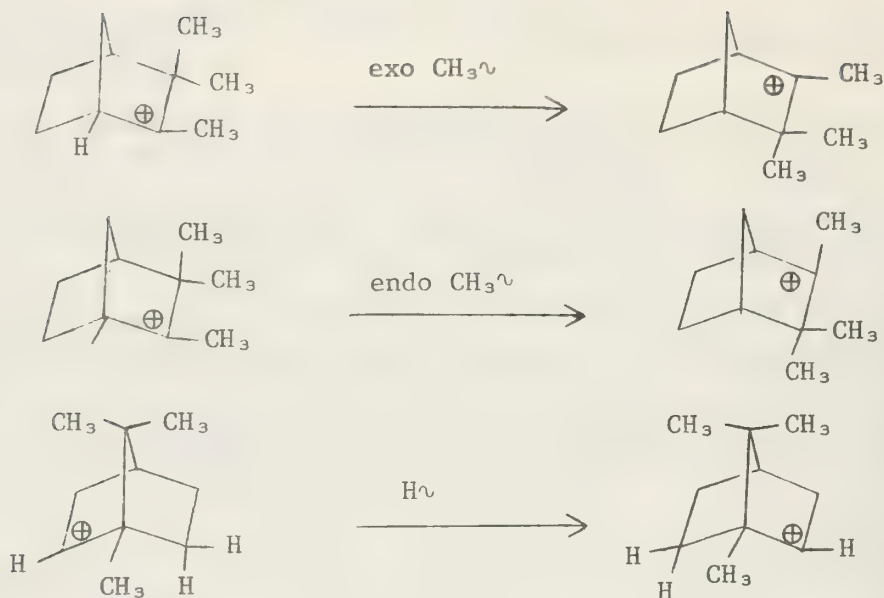


Figure 2



BIBLIOGRAPHY

1. T. S. Sorensen, *Acc. Chem. Res.*, **9**, 257 (1976).
2. H. Meerwein and K. Van Emster, *Ber.*, **55**, 2500 (1922).
3. F. C. Whitmore, *J. Am. Chem. Soc.*, **54**, 3274 (1932).
4. H. Burton and C. K. Ingold, *J. Chem. Soc.*, 904 (1928).
5. P. S. Skell and R. J. Maxwell, *J. Am. Chem. Soc.*, **84**, 3963 (1962).
6. T. S. Sorensen and K. Ranganayakulu, *Tetrahedron Lett.*, 659 (1970).
7. C. D. Poulter and S. Winstein, *J. Am. Chem. Soc.*, **91**, 3649, 3650 (1969).
8. C. D. Poulter and S. Winstein, *ibid.*, **94**, 2297 (1972).
9. J. D. Roberts and J. A. Yancey, *J. Am. Chem. Soc.*, **75**, 3165 (1953).
10. W. R. Vaughan and R. Perry, *J. Am. Chem. Soc.*, **75**, 3168 (1953).
11. W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. L. Warren, *J. Am. Chem. Soc.*, **85**, 2282 (1963).
12. C. W. David, B. W. Everling, R. J. Kilian, J. B. Stothers, and W. R. Vaughan, *ibid.*, **95**, 1265 (1973).
13. E. Huang, K. Ranganayakulu, and T. S. Sorensen, *J. Am. Chem. Soc.*, **94**, 1780 (1972).
14. R. Haseltine, E. Huang, K. Ranganayakulu, and T. S. Sorensen, *Can. J. Chem.*, **53**, 1056 (1975).
15. R. P. Haseltine and T. S. Sorensen, *Can. J. Chem.*, **53**, 1057 (1975).
16. R. S. Bly and H. L. Dryden, *Chem. Ind. (London)*, 1287 (1959).
17. C. F. Wilcox and S. S. Chibber, *J. Org. Chem.*, **27**, 2332 (1962).
18. F. Cramer and W. Rittersdorf, *Tetrahedron*, **23**, 3015 (1967).
19. G. LeNy, *C. R. Hebd. Seances Acad. Sci.*, **251**, 1526 (1960).
20. R. Haseltine, E. Huang, K. Ranganayakulu, T. S. Sorensen, and N. Wong, *Can. J. Chem.*, **53**, 1876 (1975).

APPROACHES TO THE COBALAMIN-DEPENDENT REARRANGEMENTS: SPECTROSCOPY AND MODEL STUDIES

Reported by Roger A. Brown

October 25, 1976

Introduction. Prior to 1922, pernicious anemia was almost always fatal, but in that year it was discovered that the disease could be treated by feeding the patient large quantities of liver. This continued to be the prescription until 1948, when the active agent in liver was isolated: a red crystalline compound which effectively treated the disease in dosages of only 1-2 μg per day (much to the relief of pernicious anemics). When the structure of the natural form of this compound was determined in 1961 by X-ray crystallography, it was found to be 5'-deoxyadenosylcobalamin (Figure 1).^{1a}

When the vitamin was first isolated, the 5'-deoxyadenosyl group was unwittingly replaced during isolation by cyanide ion. In rigorous usage, Vitamin B₁₂ means cyanocobalamin, whereas Vitamin B₁₂ co-enzyme is used to designate the 5'-deoxyadenosyl derivative. The tetrapyrrole macrocycle occupying the four equatorial coordination sites of the cobalt ion is known as the corrin ring system. If the benzimidazole base is coordinated in the sixth site, the system (irrespective of the ligand occupying the axial fifth site) is a "base-on" cobalamin; should the base dissociate, it is a "base-off" cobalamin. Cobinamides are formally derived from cobalamins by hydrolysis of the benzimidazole ribonucleotide. In aqueous solution, the sixth site of cobinamides is hydrated. Throughout this abstract, base-on cobalamins will be abbreviated as $\uparrow[\text{Co}]$, base-off cobalamins as $\downarrow[\text{Co}]$,

and cobinamides as $[\text{Co}]$; $-\text{CH}_2\text{R}$ will represent the 5'-deoxyadenosyl residue. Cleavage of the cobalt-carbon bond can proceed formally by three different pathways. Heterolytic cleavage may occur, either to a carbanion and Co(III) cation or to a carbonium ion and Co(I) anion. Alternatively, cleavage in a homolytic fashion would produce a carbon radical and a paramagnetic Co(II) species. Cob(I)alamin is known as B_{12s}, cob(II)alamin as B_{12r} and cob(III)-alamin is observed in aqueous solution as hydroxocobalamin, B_{12b}. (Figure 2)

Figure 1. Vitamin B₁₂ coenzyme

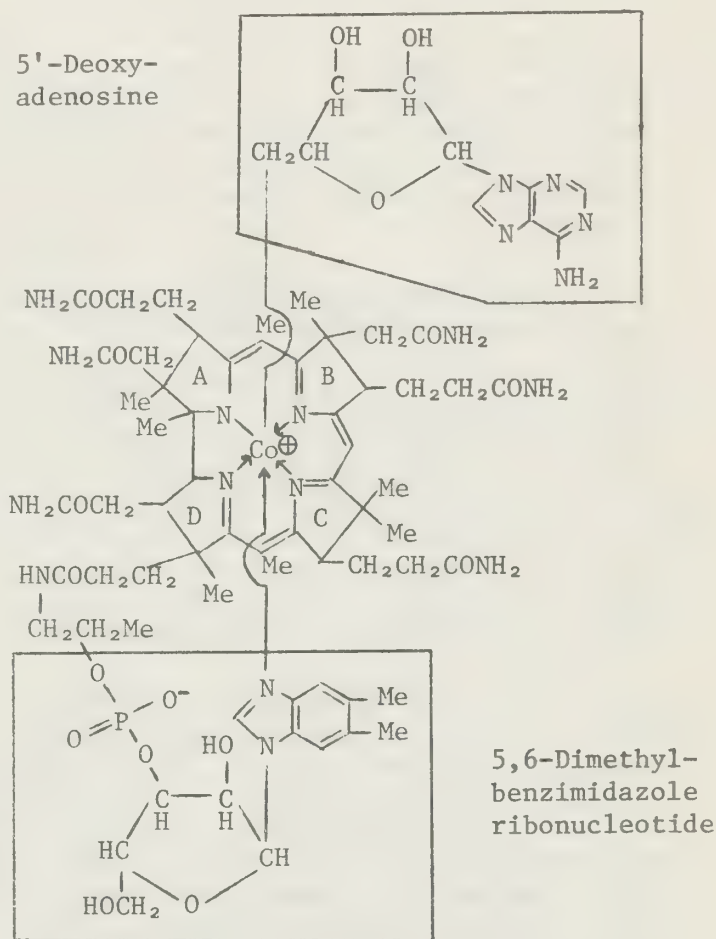
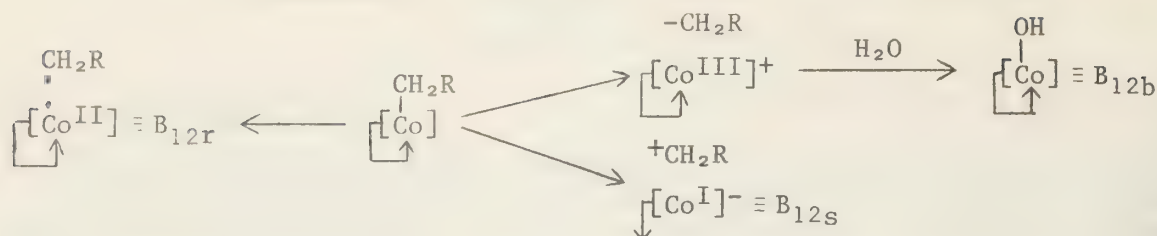


Figure 2. Cobalamin Co-C bond cleavages

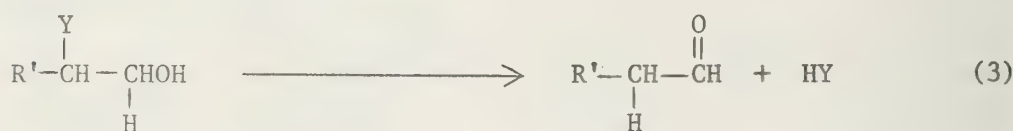


Coenzyme B₁₂ is now known to be an obligatory cofactor for nine enzymes, each of which effects a formal 1,2 migration of some group, R, between two specific carbon atoms of a substrate with concomitant counter-migration of hydrogen (eq. 1). Since the discovery of these remarkable rearrangements, research has been directed toward attempts to elucidate the mechanism(s) of the isomerizations.¹



These systems are of potential interest to organic chemists, both as a mechanistic problem and as a possible synthetic tool. A detailed understanding of the mechanism may stimulate the development of related catalysts capable of effecting similar rearrangements. To this end, a summary is presented of relevant mechanistic studies, emphasizing spectroscopic investigations and model reactions.

I. Properties of the Rearrangements. The rearrangements catalyzed by the cobalamin-dependent enzymes are of two basic types, reversible (represented by equation 2) and irreversible (represented by equation 3). The latter involve the migration of a hydroxyl or amino group to a carbon already



bearing an -OH functionality, producing a gem-diol or α-amino alcohol. The products obtained, then, are the aldehyde and water or ammonia. Since these enzymes do not catalyze the back-reaction to 1,2-diols or β-amino alcohols, the reactions are termed irreversible. The reversible reactions, on the other hand, will produce a mixture of the two isomers, starting with either one. The migrating R group is an amino, alkyl or thioester group. Note that these migrations (eq. 2) occur to an unactivated methyl group.

Various features of the reactions have been investigated and the results are summarized in Table 1. The data presented were obtained from labelling studies with ²H, ³H, ¹³C or ¹⁴C isotopes. The identity of the migrating group is unambiguous only in the diol and glycerol dehydrase reactions; in three of the others, it was determined by appropriate labelling experiments. To study the stereochemistry of the hydrogen migration, chiral isotopically labelled substrates were prepared; the products of enzymatic activ-

TABLE 1.^x General Characteristics of the Rearrangements

Enzyme	Reaction Type**	R or Y	R'	Migrating Group	Retention(+) or Inversion(-) [Ⓔ]	Non-Exchange with Solvent Hydrogen	H-transfer via C-5'
Methylmalonyl-CoA Mutase	Rev.	$\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{SCoA} \end{array}$	$-\text{CO}_2\text{H}$	R (1g)	+ (1g)	(1g)	(1g)
Glutamate Mutase	Rev.	$\begin{array}{c} \text{NH}_2 \\ \\ -\text{CH}-\text{CO}_2\text{H} \end{array}$	$-\text{CO}_2\text{H}$	R (1g)	- (1g)	(1g)	(1g)
α -Methylene-glutarate Mutase	Rev.	$\begin{array}{c} \text{CH}_2 \\ \\ -\text{C}-\text{CO}_2\text{H} \end{array}$	$-\text{CO}_2\text{H}$	nr	nr	(1g)	(1g)
Ornithine Mutase	Rev.	$-\text{NH}_2$	$\begin{array}{c} \text{NH}_2 \\ \\ -\text{CH}_2-\text{CH}-\text{CO}_2\text{H} \end{array}$	nr	nr	nr	nr
D- α -Lysine Mutase	Rev.	$-\text{NH}_2$	$\begin{array}{c} \text{NH}_2 \\ \\ -(\text{CH}_2)_2-\text{CH}-\text{CO}_2\text{H} \end{array}$	nr	nr	nr	(11)
L- β -Lysine Mutase	Rev.	$-\text{NH}_2$	$\begin{array}{c} \text{NH}_2 \\ \\ -\text{CH}_2-\text{CH}-\text{CH}_2\text{CO}_2\text{H} \end{array}$	nr	nr	(1j)	(11)
Ethanolamine Deaminase	Irrev.	$-\text{NH}_2$	$-\text{H}, -\text{CH}_3$	Y (11)	\dagger (2)	(1i)	(1i)
Diol Dehydrase	Irrev.	$-\text{OH}$	$-\text{H}, -\text{CH}_3$	Y	- (1j)	(1j)	(1g)
Glycerol Dehydrase	Irrev.	$-\text{OH}$	$-\text{H}, -\text{CH}_3, -\text{CH}_2\text{OH}$	Y	nr	nr	(1i)

*nr = not reported; () indicates reference number

**Rev. = reversible (eq. 2); Irrev. = irreversible (eq. 3)

[Ⓔ]retention or inversion of configuration at the carbon to which hydrogen migrates

ity were then examined for optical activity by comparison with authentic optically pure samples of the products. For some of the enzymes, it has been shown that the migrating hydrogen does not exchange with solvent hydrogen; tritium is not released to solvent from labelled substrate upon reaction, nor is tritium incorporated in unlabelled substrate when the reaction is performed in tritiated water. The involvement of 5'-deoxyadenosine in this migration has been demonstrated. Tritium exchange between substrate and the 5' carbon of the deoxyadenosyl residue was reported for all but one of the enzymes.

The enzymes exhibit a large degree of similarity with regard to many aspects of their activity, but not the stereochemistry of hydrogen migration. The ethanolamine deaminase reaction proceeds with racemization, whereas glutamate mutase and diol dehydrase both effect inversion and methylmalonyl-CoA mutase causes isomerization with retention of configuration. Whether these differences result from the local chemical environment of the active site of the enzyme or are a consequence of specific cobalamin chemistry is a question that remains to be answered. Other questions, concerning the oxidation state of cobalt, the importance of base-on — base-off equilibria, and the relevance of various model systems, will be reviewed.

II. Oxidation State of Cobalt. The fact that the 5' carbon of deoxyadenosine functions as an intermediate hydrogen carrier necessitates cleavage of the cobalt-alkyl bond during catalysis. Thus, denaturation of an enzyme engaged in catalysis could reasonably be expected to result in the release to solvent of free 5'-deoxyadenosine. The isolation of this compound has been reported for methylmalonyl-CoA mutase,³ L- β -lysine mutase,⁴ ethanolamine deaminase,⁵ and diol dehydrase.⁶ The yields, where reported, vary consider-

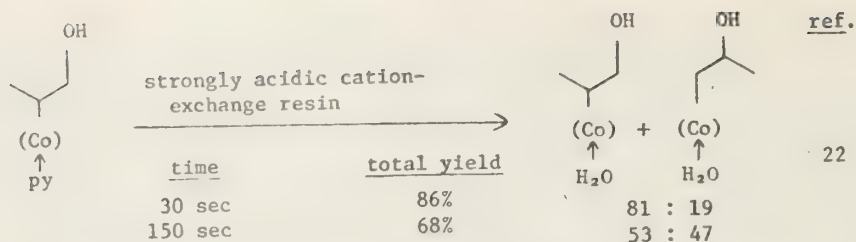
ably, from 15%³ to nearly quantitative.^{5c} When substrate analogs are used,^{5a,5a,c} the amount of 5'-deoxyadenosine isolated increases stoichiometrically with enzyme deactivation. In the most reliable work, 5'-[5'-¹⁴C] deoxyadenosylcobalamin was used as coenzyme and the radioactive material which was isolated by liquid chromatography following denaturation was shown to possess TLC behavior in three solvent systems identical to authentic 5'-deoxyadenosine. These results provide evidence that the Co-5'C bond is indeed cleaved. The question now arises, in what manner does cleavage occur? Mechanistic proposals have been advanced which assign the role of catalytic agent to $[Co^{III}]^+$, B_{12r} , or B_{12s} . The basis for these proposals stems from various $[Co^{III}]^+$ kinds of evidence. The likelihood of each oxidation state has been inferred from one model system or another. Consider first the evidence provided by spectroscopy.

The uv-vis absorption spectra of base-on coenzyme, base-off coenzyme, base-on B_{12r} , base-off B_{12r} and B_{12s} are all different.⁷ (B_{12s} apparently exists only in a base-off state.) Note that these spectra are of only the coenzyme; no enzyme is present. When an absorption spectrum of the coenzyme/enzyme/substrate steady state is obtained for diol dehydrase with 1,2-propanediol, it resembles most closely that of base-on B_{12r} , but the match is not exact. By plotting difference spectra vs. base-on coenzyme, it becomes immediately obvious from the 600-1000nm range that base-on B_{12r} is present. These findings are representative of uv-vis spectral work reported.

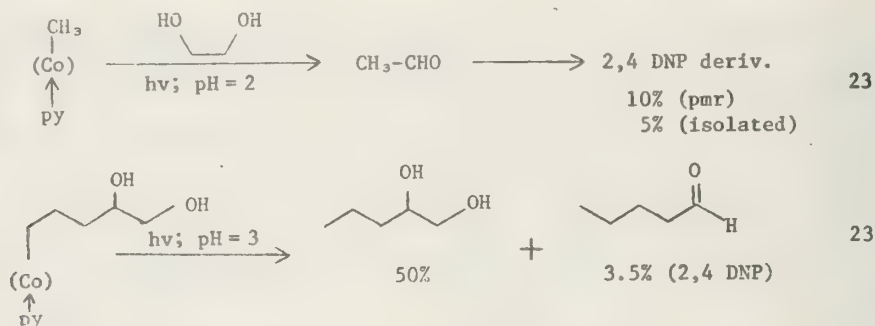
The technique is subject to the fault that all B_{12} oxidation states absorb in the uv-vis region. Inferring from an observed spectrum the presence of one particular species when the match is not exact may lead to erroneous conclusions. A more reliable method for detecting the presence of B_{12r} is the use of epr (electron paramagnetic resonance) spectroscopy. The epr spectrum of B_{12r} has been studied⁸ in the absence of any enzyme and is well-characterized. Epr spectroscopy provides a potent investigative tool for the detection of B_{12r} intermediates in catalytic systems. Caution should be exercised in the interpretation of these spectra, however, since both B_{12s} and $[Co^{III}]^+$ are transparent to the technique. The mere presence of B_{12r} during catalysis does not demand its involvement in the catalysis; epr signals would still result if B_{12s} or $[Co^{III}]^+$ were the actual catalyst and B_{12r} were present in only small quantity. Or, the reactions may proceed by a sequence involving more than one oxidation state of cobalt. Such formal possibilities must at least be considered.

Epr signals are observed when ethanolamine deaminase,^{9,10} diol dehydrase,¹¹ and glycerol dehydrase¹² are engaged in catalysis. (Only for these irreversible systems have epr signals been reported; whether this is a feature unique to these systems, or a consequence of limited investigation is unclear.) The appearance of epr signals has been shown not only to coincide with enzymatic activity,¹³ but also to be kinetically competent with product formation^{11c} in at least one case. Thus, it is reasonable to postulate the intermediacy of B_{12r} species in these reactions.

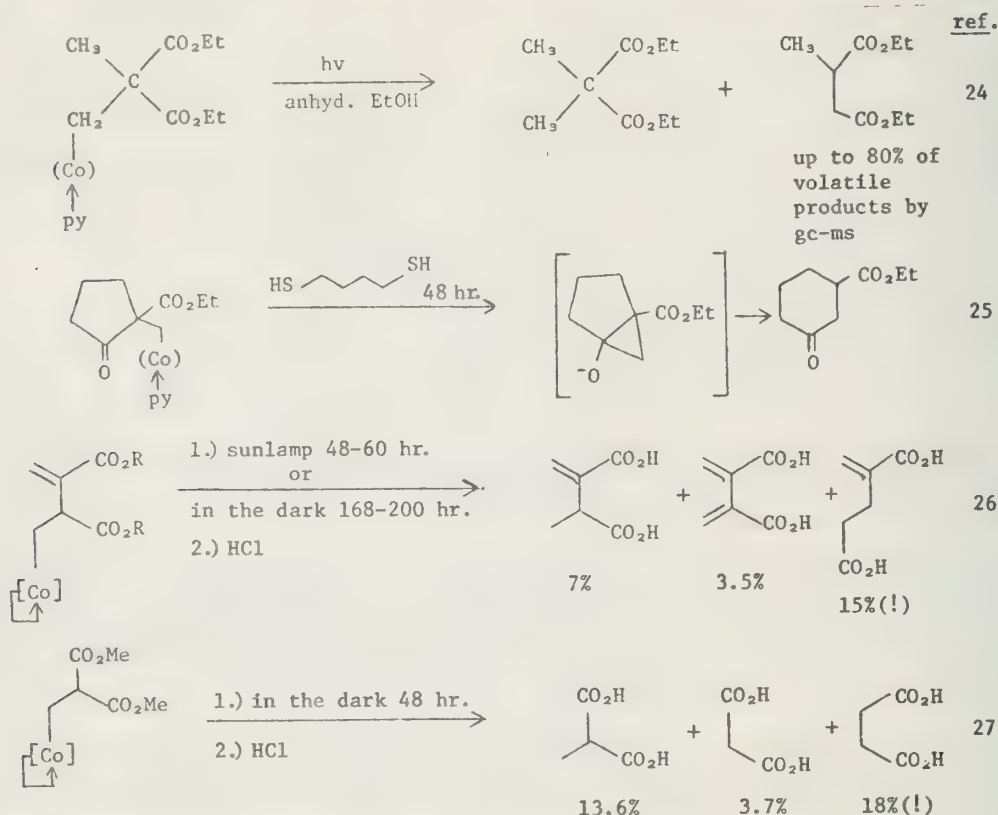
In summary, spectral evidence suggests that the mechanism of at least these irreversible reactions involves B_{12r} as a catalytic intermediate. Nevertheless, substantial evidence, which derives primarily from model reactions, exists for other mechanisms.



The acid-catalyzed isomerization of β -hydroxyalkylcobalamins²² is a model for the diol reactions. Other models²³ for these reactions appear to involve radical mechanisms, since they are initiated by irradiation, a process which is known to induce homolytic cleavage of the Co-C bond in alkylcobaloximes.



Model reactions for methylmalonyl-CoA mutase and α -methyleneglutarate mutase have also been put forward.



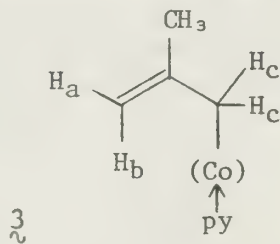
The last two reactions (ref. 26 & 27) are especially significant, since they involve cobalamin derivatives of actual enzyme substrates. These results strongly suggest that it is cobalamin chemistry which directs the course of these reactions.

IV. Proposed Mechanisms. There are common themes in most of the mechanisms which have been proposed. Generally, the cobalt-alkyl bond is pictured to break in some fashion and the 5'-deoxyadenosyl radical or ion so formed abstracts a hydrogen from substrate. The Co-substrate ion or radical pair then interact in some manner so as to effect isomerization. After dissociation from the cobalamin group, the product radical or ion abstracts one of the hydrogens from the 5' methyl of deoxyadenosine, following which 5'-deoxyadenosylcobalamin may reform.

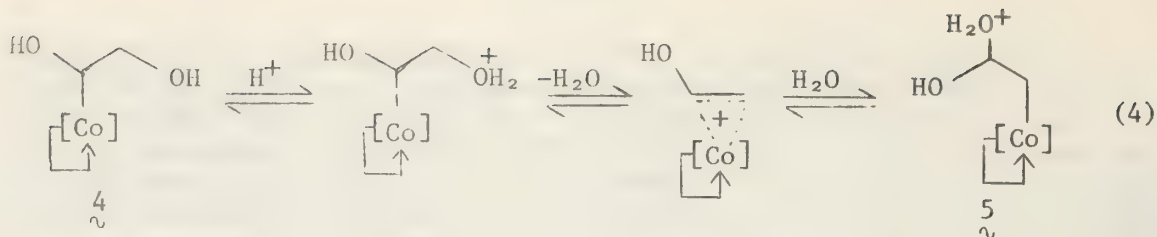
One aspect of the general mechanism is the potential importance of axial base coordination. In one study,²⁸ the chemical shifts of substituents on the corrin ring in cobalamins were studied in relation to the base-on and base-off forms. From comparison of the pmr spectrum of B_{12S} with those studied, it was concluded that the axial base in the anionic complex is not coordinated to the cobalt ion. This is reasonable, since coordination of the base would act to destabilize the complex by donation of electron density into an already electron-rich region.

The significance of this consideration was underscored by a cyclic voltammetry study²⁹ from which it was concluded that any mechanism involving B_{12S} in the isomerization must also involve a prior dissociation of the benzimidazole base. Conversely, any evidence for a catalytically active base-on cobalamin would tend to rule out B_{12S} as an important intermediate.

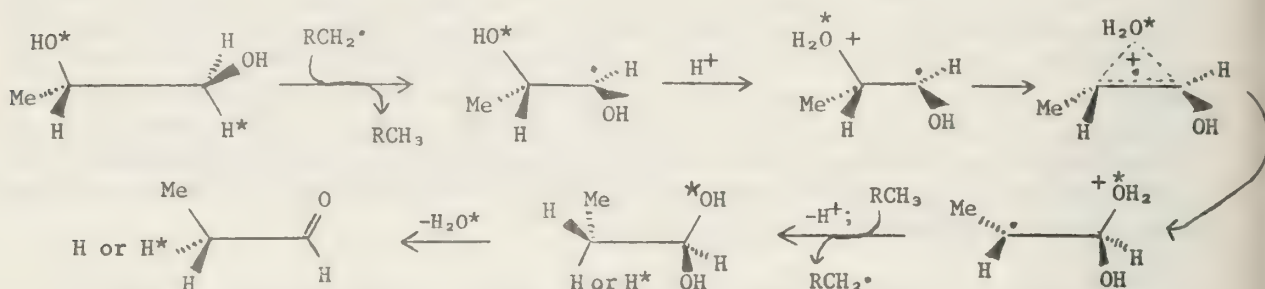
In a cobaloxime system, evidence for the interdependence of axial ligation of pyridine and the labilization of the cobalt-carbon bond has been reported.³⁰ The 100 MHz pmr spectrum of λ in CDCl₃ at -6° shows two singlets for the vinyl protons H_a and H_b, and a singlet for the methylene protons H_c, as well as a clean doublet for the ortho protons on the pyridine ring. At 56°, the signal for the ortho protons has broadened and the signals of H_a, H_b and H_c have nearly coalesced. This indicates that the allylic ligand is undergoing an exchange process which equilibrates H_a, H_b and H_c to an average magnetic environment as the temperature is raised. The broadening of the ortho protons signal suggests a similar labilization of the coordinated pyridine. In a 60 MHz spectrum of 2-methylallyl(aquo)cobaloxime (λ with water replacing pyridine), a sharp 4-proton singlet assigned to H_{a,b,c} collapses to baseline on addition of three equivalents of pyridine, indicating that the rapid exchange which makes H_a, H_b and H_c equivalent on the pmr time scale in the aquo derivative has been slowed by the addition of the more strongly complexing pyridine. Presumably, cooling the sample to -6° would cause singlets for H_a, H_b and H_c to emerge from the baseline as the non-equivalent limit is reached. These data indicate that dissociation of the axial base favors labilization of the alkyl group.



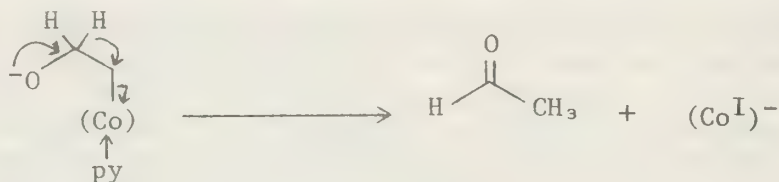
Almost every paper dealing with the B₁₂ coenzyme or models proposes a mechanism for the isomerization reactions. Representative examples of mechanisms proposed for the conversion of ethylene glycol to acetaldehyde will suffice to indicate essential features. As already mentioned, Dolphin has evidence he believes supports a Co(III) π -complex intermediate. As applied to the diol dehydrase reaction, this concept results in equation 4.³¹ The proposal is not necessarily inconsistent with the epr evidence for a B_{12r} intermediate, since λ could be formed by and λ could cleave by a radical mechanism.



It has also been postulated that the rearrangement may proceed via a radical process catalyzed by acid.³²



Finally, on the basis of the observed formation of acetaldehyde from β -hydroxyethylcobaloximes in alkaline solution,³³ Schrauzer has proposed that Co(I) is a likely intermediate in the diol dehydrase reaction.



BIBLIOGRAPHY

- (a) B. M. Babor, *Accts. Chem. Res.*, **8**, 376 (1975); (b) R. H. Abeles and D. Dolphin, *ibid.*, **9**, 114 (1976); (c) E. I. Ochiai, *J. Nucl. Inorg. Chem.*, **37**, 351 (1975); (d) G. N. Schrauzer, *Prog. Chem. Org. Nat. Prod.*, **31**, 583 (1974); (e) R. J. Sundberg and R. Bruce Martin, *Chem. Rev.*, 471 (1974); (f) A. S. Mildvan, *Ann. Rev. Biochem.*, **43**, 357 (1974); (g) H. A. Barker in "The Enzymes", P. Boyer, ed., 3rd ed., Vol. VI, Academic Press, New York, 1972; (h) T. C. Stadtman, *ibid.*, Vol. VI; (i) H. A. Barker, *Ann. Rev. Biochem.*, **41**, 55 (1972); (j) H. P. C. Hogenkamp, *Ann. Rev. Biochem.*, **37**, 225 (1968).
- J. Retey, C. J. Suckling, D. Arigoni and B. M. Babor, *J. Biol. Chem.*, **249**, 6359 (1974).
- B. M. Babor, A. D. Woodams and J. D. Brodie, *ibid.*, **248**, 1445 (1973).
- J. C. Baker, C. van der Drift and T. C. Stadtman, *Biochemistry*, **12**, 1054 (1973).
- (a) B. M. Babor, *J. Biol. Chem.*, **245**, 1755 (1970); (b) T. J. Carty, B. M. Babor and R. H. Abeles, *ibid.*, **246**, 6313 (1971); (c) B. M. Babor, T. J. Carty and R. H. Abeles, *ibid.*, **249**, 1689 (1974).
- (a) O. W. Wagner, H. A. Lee, Jr., P. A. Frey and R. H. Abeles, *ibid.*, **241**, 1751 (1966); (b) M. Jayme and J. H. Richards, *Biochem. Biophys. Res. Commun.*, **43**, 1329 (1971); (c) T. H. Finlay, J. Valinsky, K. Sato and R. H. Abeles, *J. Biol. Chem.*, **247**, 4197 (1972).
- M. A. Foster, H. A. O. Hill and R. J. P. Williams, *Biochem. Soc. Symp.*, **31**, 187 (1970).

8. (a) S. A. Cockle, H. A. O. Hill, J. M. Pratt and R. J. P. Williams, *Biochim. Biophys. Acta*, 177, 686 (1969); (b) J. H. Bayston, F. D. Looney, J. R. Bilbrow and M. E. Winfield, *Biochemistry*, 9, 2164 (1970).
9. (a) B. M. Babior, T. H. Moss and D. C. Gould, *J. Biol. Chem.*, 247, 4389 (1972); (b) B. M. Babior, T. H. Moss, W. H. Orme-Johnson and H. Beinert, *ibid.*, 249, 4537 (1974).
10. P. Y. Law, D. G. Brown, E. L. Lien, B. M. Babior and J. M. Wood, *Biochemistry*, 10, 3428 (1971).
11. (a) T. H. Finlay, J. E. Valinsky, A. S. Mildvan and R. H. Abeles, *J. Biol. Chem.*, 248, 1285 (1973); (b) J. E. Valinsky, R. H. Abeles and A. S. Mildvan, *ibid.*, 249, 2751 (1974); (c) J. E. Valinsky, R. H. Abeles and J. A. Fee, *J. Am. Chem. Soc.*, 96, 4709 (1974).
12. S. A. Cockle, H. A. O. Hill, R. J. P. Williams, S. P. Davies and M. A. Foster, *ibid.*, 94, 275 (1972).
13. B. M. Babior and D. C. Gould, *Biochem. Biophys. Res. Commun.*, 34, 441 (1969).
14. G. N. Schrauzer and J. Kohnle, *Chem. Ber.*, 97, 3056 (1964).
15. (a) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, 89, 1999 (1967); (b) G. N. Schrauzer, *Adv. Chem. Ser.*, 100, 1 (1971); (c) G. N. Schrauzer, *Accts. Chem. Res.*, 1, 97 (1968).
16. B. T. Golding, H. L. Holland, U. Horn and S. Sakrikar, *Angew. Chem., Int. Ed. Eng.*, 9, 959 (1970).
17. C. A. Bunton and A. Konasiewicz, *J. Chem. Soc.*, 1354 (1955).
18. B. T. Golding and S. Sakrikar, *J. Chem. Soc., Chem. Commun.*, 1183 (1972).
19. R. B. Silverman, D. Dolphin and B. M. Babior, *J. Am. Chem. Soc.*, 94, 4028 (1972).
20. R. B. Silverman and D. Dolphin, *ibid.*, 98, 4633 (1976), and references therein.
21. T. M. Vickrey, R. N. Katz and G. N. Schrauzer, *ibid.*, 97, 7248 (1975), and references therein.
22. K. L. Brown and L. L. Ingraham, *ibid.*, 96, 7681 (1974).
23. B. T. Golding, T. J. Kemp, E. Nocchi and W. P. Watson, *Angew. Chem., Int. Ed. Eng.*, 14, 813 (1975).
24. G. Bidlingmaier, H. Flohr, U. M. Kempe, T. Krebs and J. Retey, *ibid.*, 14, 822 (1975).
25. J. N. Lowe and L. L. Ingraham, *J. Am. Chem. Soc.*, 93, 3801 (1971).
26. P. Dowd, M. Shapiro and K. Kang, *ibid.*, 97, 4754 (1975).
27. P. Dowd and M. Shapiro, *ibid.*, 98, 3724 (1976).
28. (a) J. D. Brodie and M. Poe, *Biochemistry*, 10, 914 (1971); (b) J. D. Brodie and M. Poe, *ibid.*, 11, 2534 (1972).
29. (a) P. G. Swetik and D. G. Brown, *Biochim. Biophys. Acta*, 343, 641 (1974); (b) see also T. M. Kenyhercz, T. P. DeAngelis, B. J. Norris, W. R. Heineman and H. B. Mark, Jr., *J. Am. Chem. Soc.*, 98, 2469 (1976) D. Lexa and J. M. Saveant, *ibid.*, 98, 2652 (1976).
30. D. Dodd and M. D. Johnson, *ibid.*, 96, 2279 (1974). For recent studies on the kinetics and mechanism, see K. L. Brown, D. Lyles, M. Pencovici and R. G. Kallen, *ibid.*, 97, 7338 (1975); F. R. Jensen and R. C. Kiskis, *ibid.*, 97, 5820 (1975).
31. R. B. Silverman and D. Dolphin, *J. Am. Chem. Soc.*, 98, 4626 (1976).
32. B. T. Golding and L. Radom, *J. Chem. Soc., Chem. Commun.*, 939 (1973). For supporting work, see B. C. Gilbert, L. P. Larkin and R. O. C. Norman, *J. Chem. Soc., Perkin II*, 794 (1972); C. Walling and R. A. Johnson, *J. Am. Chem. Soc.*, 97, 2405 (1972); B. T. Golding and L. Radom, *ibid.*, 98, 6331 (1976).
33. G. N. Schrauzer and J. W. Sibert, *ibid.*, 92, 1022 (1970).

α -ARYLATION OF KETONES

Reported by Kenneth J. Allison

November 1, 1976

Enolates react easily with alkyl halides, via nucleophilic displacement, to yield α -alkylated carbonyl compounds. Aryl halides, however, unless strongly activated by electron-withdrawing groups, fail to react under the conditions required for α -alkylation, thus requiring alternative procedures for α -arylation which will be discussed in this seminar.

One general approach to the synthesis of α -arylated ketones involves the combination of a nucleophilic α -carbon atom, as in an enolate or enamine, with a relatively electrophilic aryl species, although some mechanisms involve radical intermediates. Very reactive aryl halides, such as 2,4-dinitrochlorobenzene, have long been known to undergo nucleophilic substitution with enolates of β -dicarbonyl compounds.¹ They also react with enamines,² giving α -aryl ketones in high yield upon hydrolysis. Less reactive aryl halides, such as 4-nitrochlorobenzene, did not react with enamines, except at high temperature to yield products resulting from N-arylation.

Nitro substituents, however, may present the drawback of being difficult to remove. An easily removable, complexed chromium tricarbonyl unit can activate benzene³ and halobenzenes⁴ toward nucleophilic substitution by reducing the electron density of the ring. Using this complex, Semmelhack efficiently phenylated strongly basic carbanions and tertiary ester enolate carbanions, but methyl ketone enolates gave poor yields of arylated products. The use of nickel complexes in the reaction of enolates with aryl halides was also investigated by Semmelhack,⁵ who obtained α -arylation yields of about 30%, including an intramolecular arylation in his cephalotaxinone synthesis.⁶

Benzyne intermediates, usually generated by the reaction of halobenzenes with excess amide ion in liquid ammonia, react with ketone enolates to produce α -arylated ketones, generally in yields of 30% to 70%.⁷⁻⁹ Enamines, however, gave low to moderate yields of α -arylated products in their reactions with benzyne.^{2,9} Side products resulting from cyclization or ring amination are often abundant in these benzyne reactions.

The photostimulated aromatic $S_{RN}1$ reaction^{10,11} between some enolates and aryl halides has afforded high yields of α -arylated ketones, including an intramolecular arylation in the synthesis of cephalotaxinone.⁶ The reaction, initiated by near-ultraviolet light, is postulated to involve radical intermediates. The arylation of enolates in moderate yield by diaryliodonium salts is also believed to occur via radical intermediates.¹² The attempted arylation of enamines by diaryliodonium chloride produced poor results.²

As an alternative to the reactions between an enolate anion or its equivalent and an electron-deficient aryl species, one could consider synthetic approaches involving the opposite charge affinity relationship, i.e. between aryl carbanion equivalents and α -keto carbonium ion equivalents, such as α -halo ketones, α,β -epoxy ketones, and analogous compounds.

α -Halo ketones, which often may be regiospecifically generated,¹³ have long been known to react with aryl Grignard reagents to provide α -aryl ketones after pinacol rearrangement of the initially formed halohydrin.¹⁴ α -Aryl- α,β -unsaturated ketones have recently been synthesized in moderate yields

from the reaction of aryl Grignard reagents with the N,N-dimethylhydrazones of α,β -epoxy ketones.¹⁵ Brown and Rogic¹⁶ obtained α -aryl ketones in high yield from the base-catalyzed reaction of arylborane derivatives with α -bromo ketones.

Arylcopper reagents can add to Michael substrates produced from certain nitrogen derivatives of ketones. One such substrate is the sulfonylazo olefin system, formed by the reaction of base with an α -halo sulfonylhydrazone.¹⁷ Sacks and Fuchs¹⁸ found that the conjugate addition of arylcopper reagents to tosylazo olefins occurs readily to give α -aryl tosylhydrazones which form α -aryl ketones after carbonyl exchange¹⁹ in overall yields of about 70%. α,β -Epoxy tosylhydrazones react with arylcopper reagents to provide α -aryl- α,β -unsaturated ketones²⁰ in high yield after carbonyl exchange. A similar procedure involving the reaction of alkylcuprates with α,β -epoxy oximes might also be applied to the synthesis of α -aryl- α,β -unsaturated ketones.²¹

Friedel-Crafts alkylation of aromatic compounds with α -chloro nitrones also show the potential of providing α -aryl ketones.²²

BIBLIOGRAPHY

1. S. S. Joshi and I. R. Gambhir, *J. Am. Chem. Soc.*, **78**, 2222 (1956); I. R. Gambhir and S. S. Joshi, *J. Org. Chem.*, **27**, 1899 (1962).
2. M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).
3. M. F. Semmelhack, H. T. Hall, M. Yoshifuji and G. Clark, *J. Am. Chem. Soc.*, **97**, 1247 (1975).
4. M. F. Semmelhack and H. T. Hall, *J. Am. Chem. Soc.*, **96**, 7091, 7092 (1974).
5. M. F. Semmelhack, R. D. Stauffer and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973).
6. M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong and L. D. Jones, *J. Am. Chem. Soc.*, **97**, 2507 (1975).
7. W. W. Leake and R. Levine, *J. Am. Chem. Soc.*, **81**, 1169 (1959).
8. P. Caubere and G. Guillaumet, *Bull. Soc. Chim. Fr.*, 4643, 4649 (1972).
9. T. Kametani, S. Noguchi, I. Agata, T. Aono, K. Kigasawa, M. Hiiragi, T. Hayasaka and O. Kusama, *J. Chem. Soc. C*, 1047, 1051 (1971).
10. J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.*, **41**, 1702 (1976); J. F. Bunnett and J. E. Sundberg, *Chem. Pharm. Bull.*, **23**, 2620 (1975).
11. R. A. Rossi, R. H. de Rossi and A. F. Lopez, *J. Am. Chem. Soc.*, **98**, 1252 (1976).
12. F. M. Beringer, W. J. Daniel, S. A. Galton and G. Rubin, *J. Org. Chem.*, **31**, 4315 (1966).
13. Examples: P. L. Stotter and K. A. Hill, *J. Org. Chem.*, **38**, 2576 (1973); R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).
14. A. S. Hussey and R. R. Herr, *J. Org. Chem.*, **24**, 843 (1959).
15. G. Stork and A. A. Ponaras, *J. Org. Chem.*, **41**, 2937 (1976).
16. H. C. Brown and M. M. Rogić, *J. Am. Chem. Soc.*, **91**, 4304, 6852 (1969).
17. L. Caglioti, P. Grasselli, F. Morlacchi and G. Rosini, *Chem. Ind. (London)*, 25 (1968); G. Rosini and R. Ranza, *J. Org. Chem.*, **36**, 1915 (1971).
18. C. E. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975).
19. C. E. Sacks and P. L. Fuchs, *Synthesis*, 456 (1976).
20. P. L. Fuchs, *J. Org. Chem.*, **41**, 2935 (1976).
21. E. J. Corey, L. S. Melvin, Jr., and M. F. Haslanger, *Tetrahedron Lett.*, 3117 (1975).
22. S. Shatzmiller, P. Gygas, D. Hall and A. Eschenmoser, *Helv. Chim. Acta*, **56**, 2961 (1973).

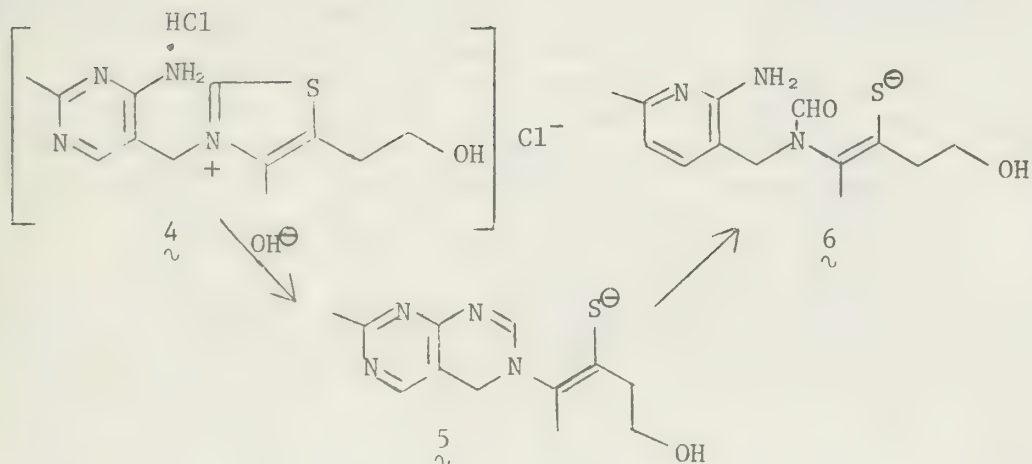
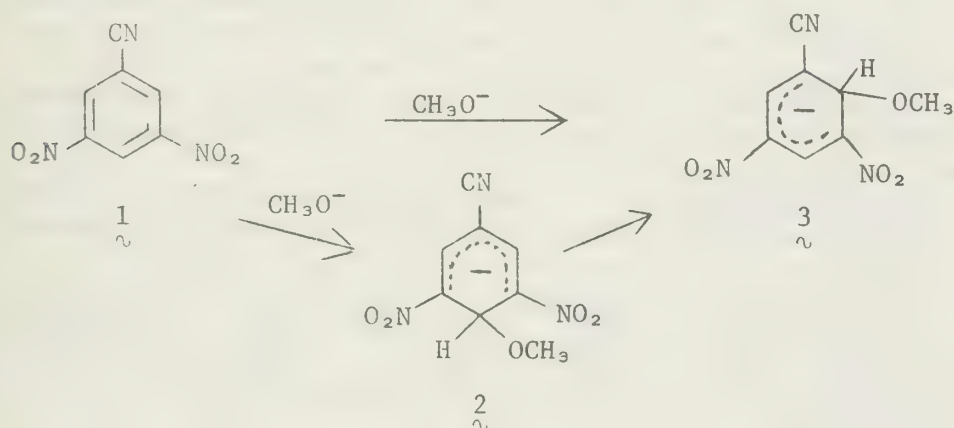
Reported by Peter L. Rinaldi

November 4, 1976

Ever since its inception, Nuclear Magnetic Resonance has been an extremely useful tool for the chemist. Many techniques have been developed to enhance its utility, one of the lesser known being the measurement of nmr signals in flowing systems. This technique has shown its usefulness for the measurement of flowrates without disturbing the flowing system,³⁻⁶ and for in stream monitoring of commercial processes.¹⁻⁷

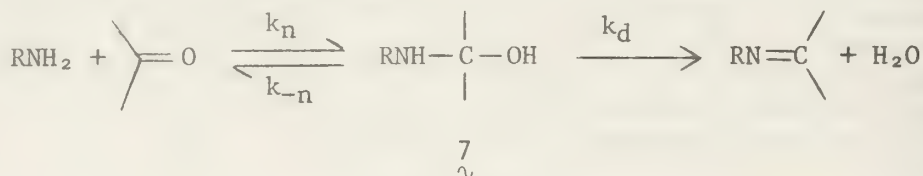
Recently the additional potential of this technique has been realized. It has been used to study several reactions, including the enzyme catalyzed hydrolysis of *t*-butyl-L-phenylalanine,⁸ the electrochemical coupling of *trans*-1-phenyl-1-butene-3-one,⁹ the oxidation of isopropyl alcohol using titanous ion with hydrogen peroxide,¹⁰ CIDNP induced by the action of aryl peroxides on phenyl halides,¹¹ and the effect of metal ions on the conformations of certain enzymes.^{12,13}

It was previously reported that the attack of methoxide on 3,5-dinitro-cyanobenzene produced intermediate **2** almost instantaneously at 33°. ¹⁴ This same reaction studied by flow nmr showed the simultaneous formation of **2** and **3** by attack of methoxide at the two nonequivalent positions on the aromatic ring. Compound **2** was found to rearrange to **3**, the thermodynamic product.



Asahi and Mizuta^{16a} studied the basic hydrolysis of thiamine hydrochloride (4), diethyl carbonate, and ethyl carbamate. Ethyl carbamate gave no detectable intermediate; however, when diethyl carbonate was mixed with a 4M solution of potassium hydroxide, an intermediate monoethyl carbonate could be observed. Thiamine hydrochloride (4) when mixed with a solution of potassium hydroxide produced an intermediate the spectrum of which was in accord with the structure previously assigned 5.^{16b} When the flow was stopped, thiol 6 appeared at the expense of this intermediate.

Kinetic data for the addition of nitrogen nucleophiles to carbonyl compounds support the initial formation of a carbinolamine (7), followed by a slower dehydration step to give the imine. Cocivera *et al.*¹⁷ have studied the addition of hydroxylamine to acetaldehyde and report a partial spectrum for the carbinolamine intermediate.



This technique coupled with Fourier Transform, could be useful to study the reactions of compounds which are only available in small quantities.⁸

BIBLIOGRAPHY

1. A. I. Zhernovoi and G. D. Latyshev, "Nuclear Magnetic Resonance in a Flowing Liquid", Consultants Bureau, New York, 1965.
2. D. W. Jones and T. F. Child, *Magnetic Resonance*, 8, 123 (1973).
3. W. K. Genthe, in "Flow: Its Measurement and Control in Science and Industry", R. B. Dowdall, ed., Vol. I, Pt. 2, p. 849, Instrument Society of America, Pitt., Pa., 1974.
4. W. H. Vander Heyden and J. F. Toschik, *ibid.*, p. 857.
5. L. R. Hirschel and L. F. Libelo, *J. Appl. Phys.*, 33, 1895 (1962).
6. O. C. Morse and J. R. Singer, *Science*, 170, 440 (1970).
7. (a) L. O. Anderson, *J. Amer. Oil Chem. Soc.*, 48, 47 (1971); (b) R. C. Walker and W. A. Bosin, *ibid.*, 48, 50 (1971); (c) T. F. Conway, *ibid.*, 48, 54 (1971); (d) W. L. Rollwitz and G. A. Persyn, *ibid.*, 48, 59 (1971); (e) F. A. Nelson, C. A. Reilly and W. E. Savage, *Ind. Eng. Chem.*, 52, 487 (1960).
8. J. J. Grimaldi and B. D. Sykes, *J. Am. Chem. Soc.*, 97, 273 (1975).
9. J. A. Richards and D. H. Evans, *Analytical Chemistry*, 47, 964 (1975).
10. M. Cocivera, *et al.*, *J. Am. Chem. Soc.*, 96, 1611 (1974).
11. M. Lehnig and H. Fischer, *Z. Naturforsch.*, 24a, 1711 (1969).
12. J. L. Sudmeier and J. J. Pesek, *Inorg. Chem.*, 10, 860 (1971).
13. (a) J. J. Grimaldi and B. D. Sykes, *J. Biol. Chem.*, 250, 1618 (1975); (b) B. D. Sykes *et al.*, *J. Am. Chem. Soc.*, 94, 7641 (1972).
14. M. I. Foreman and R. Foster, *Can. J. Chem.*, 47, 729 (1969).
15. C. A. Fyfe *et al.*, *J. Chem. Soc., Chem. Comm.*, 743 (1973).
16. (a) Y. Asahi and E. Mizuta, *Talanta*, 19, 567 (1972); (b) G. D. Maier and D. E. Metzler, *J. Am. Chem. Soc.*, 79, 4386 (1957).
17. M. Cocivera *et al.*, *J. Am. Chem. Soc.*, 98, 1573 (1976).

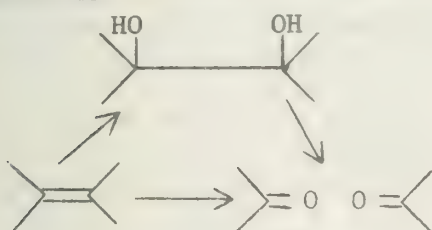
RECENTLY DEVELOPED REAGENTS FOR THE REDUCTIVE COUPLING OF CARBONYL COMPOUNDS AND RELATED REACTIONS

Reported by Daniel Heiman

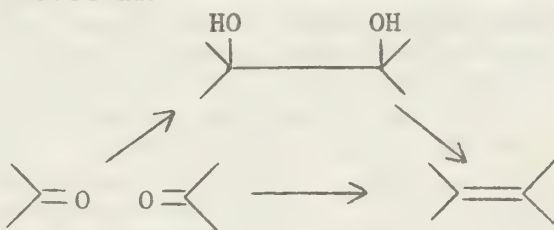
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I. Introduction. Reagents for the oxidation of olefins to vicinal diols and for the oxidative cleavage of olefins or glycols to carbonyl compounds are well known (Scheme I). Less well known are some recently developed transition metal derivatives which can effect the reversal of these transformations, that is, the reductive coupling of carbonyl compounds to olefins or pinacols and the reductive elimination of pinacols to olefins (Scheme II). This seminar will survey and evaluate these new transition metal-based reagents and compare them briefly with other reagents and techniques for performing the same conversions.

Scheme I. Oxidative Transformations



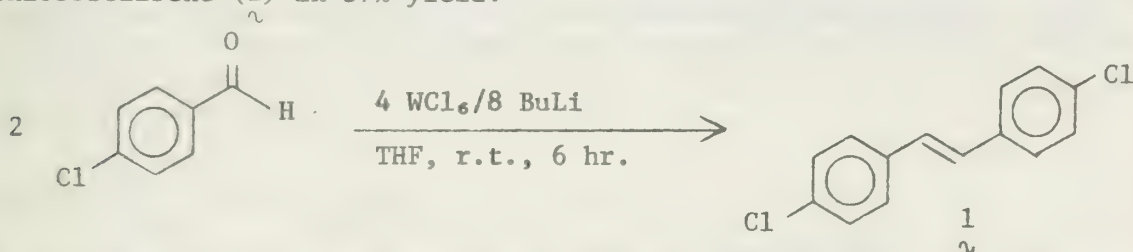
Scheme II. Reductive Transformations



II. Tungsten-Based Reagents. In 1972 Sharpless and co-workers described a series of reagents containing low-valent tungsten. One of them deoxygenates vicinal diols, and others couple ketones or aldehydes to olefins.

In one report,¹ cyclic aliphatic 1,2-diols (as the dilithium salts) were reduced to olefins with 2 molar equivalents of dipotassium tungsten hexachloride in yields ranging from 36 to 74 per cent. The principal product was usually that which would have been expected from a syn-elimination of the two hydroxyl groups, but the other geometrical isomer was always produced to some extent.

A second paper² reports reductions performed with the species produced by the reaction of tungsten (VI) chloride with two molar equivalents of butyllithium. This reagent, which was the best of eight combinations investigated, brings about the coupling of aromatic aldehydes and ketones directly to olefins in fair yield (e.g., 76% for benzaldehyde, 20% for p-cyanobenzaldehyde). A typical result was the reduction of p-chlorobenzaldehyde to p,p'-dichlorostilbene (1) in 57% yield:



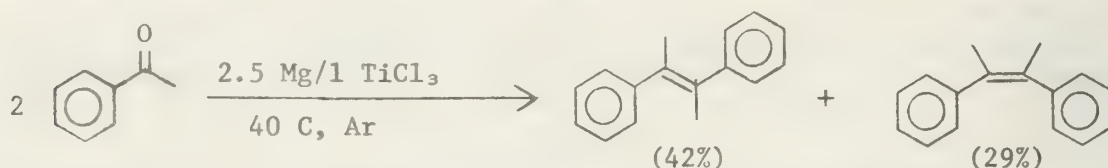
The reagent seems not to be useful for the coupling of aliphatic carbonyl compounds, since 2-butanone gave a mixture of the corresponding (E)- and (Z)-olefins in only 10% yield. However, these yields may not represent the best obtainable by this method, since M. Umbreit, one of the co-authors of the second paper, later reported³ that by increasing the reaction temperature to the reflux point of THF and lengthening the reaction time from 6 hours to 4

days, one could obtain a 78% yield of dimethylstilbene from acetophenone. This was in sharp contrast to a maximum yield of 44% for this transformation obtained with the original conditions. The product was approximately a one-to-one mixture of isomers in both cases.

The tungsten hexachloride/butyllithium reagent is also capable of reducing epoxides to olefins. Sharpless and co-workers¹ effected the deoxygenation of twelve aliphatic and aromatic oxiranes in 37 to 98% yields and with retention of stereochemistry except in the case of cis-stilbene oxide.

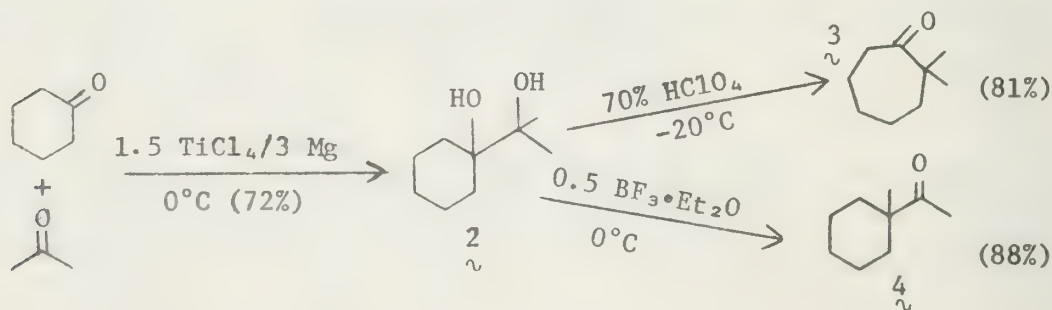
III. Titanium-Based Reagents. Some work on titanium-mediated deoxy-genative coupling of alcohols⁴ preceded the first reports that aldehydes and ketones could be reduced to olefins or pinacols by low-valent titanium.

S. Tyrlik and I. Wolochowicz first reported in 1973⁵ that the black substance formed by the reduction of titanium (III) chloride with magnesium metal would, in turn, reduce carbonyl compounds. The reaction was performed under argon, since it was known that molecular nitrogen is reduced by complexes of titanium (II). One mole of titanium chloride effected the reduction of 2 moles of carbonyl compound:

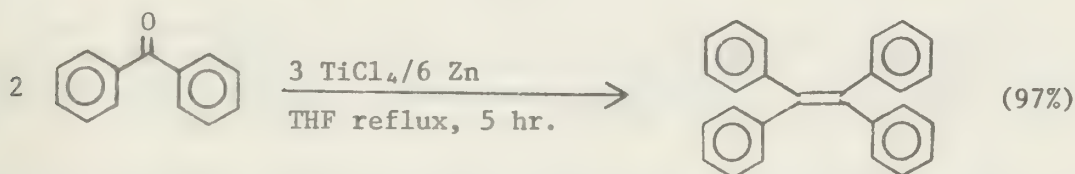


Aromatic aldehydes and ketones coupled to the corresponding olefins in 67 to 80% yields, but aliphatic compounds gave more erratic results. Acetone afforded 2,3-dimethyl-2-butene in 98% yield, but cyclohexanone gave the pinacol in 42% yield instead of the olefin. Both cis- and trans-olefins were produced in nearly equal amounts from unsymmetrical ketones or from aldehydes.

While this reagent seems not to have seen synthetic application as originally described, it has recently been proposed in slightly modified form as a pinacol coupling reagent. Corey and co-workers⁷ reduced titanium (IV) chloride with amalgamated 70 mesh magnesium and obtained a yellow-green mixture which would reduce aliphatic ketones or aldehydes to 1,2-diols in good to excellent yields (80 to 95%). With a three-fold molar excess of acetone or acetaldehyde, cross-coupled products could be obtained from cyclic ketones in preparatively useful yields (65 to 76%). Corey⁷ demonstrated some possible synthetic applications of the pinacols produced in this manner by rearrangement of the diol (2) from the crossed coupling of acetone and cyclohexanone to two different ketones (3 and 4) under different conditions.⁸



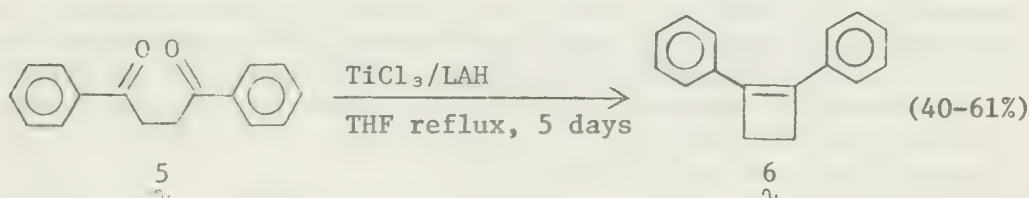
Shortly after Tyrlik's paper appeared, Mukaiyama⁹ reported that the low-valent titanium species formed by the reaction of titanium (IV) chloride with zinc powder would effect the coupling of carbonyl compounds to either pinacols or olefins, depending on the reaction conditions. The reductions were performed under argon with 1.5 moles of titanium trichloride and 3 moles of zinc per mole of carbonyl compound. From aromatic aldehydes and ketones, olefins were produced in 92 to 98% yields after four to five hours in refluxing tetrahydrofuran or dioxane.



However, if the reaction was performed at 0°C or at room temperature, pinacols were obtained instead in 91 to 98% yields. Aliphatic compounds again proved less tractable, giving only pinacols (in 78 to 86% yields) even after long reaction times. Minabe and co-workers¹⁰ have applied this reagent to the synthesis of both the pinacol and the olefin from 2-acetylfluorene, confirming the structure of some side products formed in the Clemmenson reduction of the same ketone.

The titanium reagent which has been applied most frequently in synthesis is that described in 1974 by McMurry and Fleming.¹¹ They reported that the black mixture which results from the reaction of titanium (III) chloride with lithium aluminum hydride would reduce aldehydes and ketones to olefins in refluxing tetrahydrofuran. The reaction could apparently be carried out under nitrogen without detrimental effect. Both aromatic and aliphatic carbonyl compounds afforded 80 to 95% yields of the corresponding olefins. Even the highly hindered ketone, 2-adamantanone, and the highly conjugated aldehyde, retinal, gave good yields of the corresponding olefins, 2,2'-adamantylideneadamantane and β-carotene. No comment was made on the stereochemistry of the products.

McMurry's reagent has been applied in a number of syntheses, although apparently with yields inferior to those reported in the original work. d-(+)-Camphor was coupled to a mixture of olefin isomers in 15% yield.¹² The highly hindered tetra-*iso*-propyl ethylene was prepared by two groups in 6%¹³ and 12%¹⁴ yields. (E)-4,4'-Homoadamantylidenehomoadamantane was obtained in 40% yield by Olah.¹⁵ Baumstark and co-workers¹⁶ reported the cyclization of the diketone (5) to 1,2-diphenylcyclobutene (6) with McMurry's reagent:

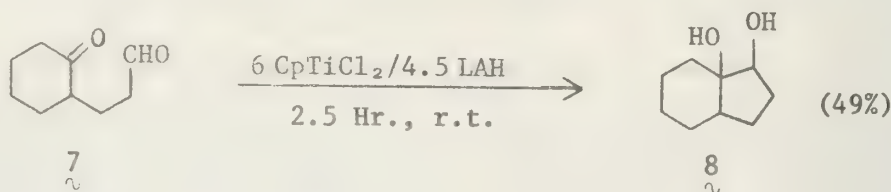


The conjugated aldehydes, (Z)- and (E)- citral, gave only 8% yields of mixed (Z and E) olefins.¹⁷ Others^{18,3} have had still less success. The difficulties seem to stem in part from the fact that different batches of titanium trichloride may give inconsistent results.¹⁹

McMurry has also coupled allylic alcohols to biallys²⁰ in 33 to 95% yields with his $\text{TiCl}_3/\text{LiAlH}_4$ reagent.

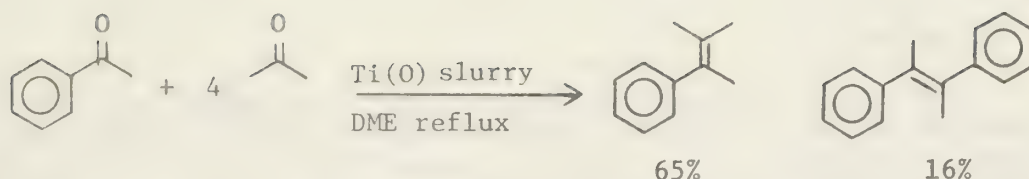
Coutts, Wailes and Martin²¹ found that cyclopentadienyl titanium (III) chloride and bromide would couple ketones and aldehydes to pinacols without the aid of a stronger reducing agent. No preparative utility was claimed for the method and no yields were given.

Corey⁷ subsequently described a combined cyclopentadienyl titanium (III) chloride/lithium aluminum hydride reagent for pinacol coupling. The reagent, prepared by the reaction of cyclopentadienyl titanium (III) chloride (CpTiCl_2) and lithium aluminum hydride in tetrahydrofuran, provided fair to good yields (32 to 60%) of cyclic diols from aliphatic keto-aldehydes and diketones. For example, the cyclohexanone derivative (7) was reduced to the bicyclic diol (8) in 49% yield.



McMurry has been aware of the problems that others have had in attempting to utilize his reagent and has worked to improve the method. He has recently reported¹⁹ that active titanium metal prepared by Rieke's method²² effects the reductive coupling of aliphatic ketones and aldehydes to olefins in 40 to 90% yields. To obtain the reagent, titanium (III) chloride and potassium metal are heated together in tetrahydrofuran prior to the addition of the carbonyl compound.

Olefins could also be obtained from vicinal diols with this reagent.¹⁹ Five di-, tri- and tetrasubstituted aliphatic 1,2-diols gave yields of olefins ranging from 55 to 85%, however, trans-decalin-9,10-diol failed to react. Acyclic starting materials, whether carbonyl compounds or pinacols, produced mixtures of olefins, and with the aromatic compounds benzaldehyde and 9-fluorenone, considerable overreduction to the saturated coupled product was observed. A further refinement of the method involves the use of lithium metal rather than potassium to reduce the titanium trichloride. With the active titanium reagent so obtained, McMurry and Krepski²³ have recently been able to carry out the crossed coupling of a number of ketones with acetone. With a four-fold excess of acetone, they obtained 50 to 94% yields of isopropylidene derivatives along with zero to 29% of self-coupled products and unspecified yields of the volatile 2,3-dimethyl-2-butene. In a typical reaction acetophenone and acetone gave 65 and 16% yields of the crossed-coupled and self-coupled products respectively, based on acetophenone.



Diaryl ketones gave primarily the crossed-coupled product even when reduced in the presence of an equimolar amount of an aliphatic ketone.

IV. Other Methods. There are a number of older methods for the reductive coupling of carbonyl compounds to pinacols which have been modified or have seen some synthetic use fairly recently.

One of these methods which also makes use of a transition metal in a low oxidation state is reduction with chromium (II) salts. In the original work on chromium (II) reductions of carbonyl compounds,²⁴ aromatic α,β -unsaturated ketones coupled at the β -carbon atom or failed to react, while α,β -unsaturated aldehydes gave the corresponding 1,2-diols in only 5 to 30% yields. In 1970, Davis and Bigelow²⁵ reported that benzaldehyde could be reduced to hydrobenzoin by this method, but the 69% yield they obtained is inferior to that obtained with the titanium reagents.

An old method for pinacol coupling which still seems to be valuable²⁶ is that of Gomberg and Bachmann,²⁷ in which an equimolar mixture of magnesium and magnesium iodide is the reducing agent. The yields they obtained for the reductive dimerization of diaryl ketones (53 to 99%) compare quite favorably with those produced by the recently developed methods.

It has been known since 1900²⁸ that the reduction of aromatic carbonyl compounds to pinacols can be effected photochemically. The reaction must be carried out in a solvent possessing labile hydrogen atoms (e.g., an alcohol), which serves as the reducing agent. Nearly quantitative yields of pinacols are obtained from simple aromatic ketones such as benzophenone.²⁹ However, the reaction is photochemically reversible, so it fails with highly hindered ketones,³⁰ and extremely low or zero quantum yields are obtained when the substrate possesses a low-lying $\pi-\pi^*$ state.³¹

A frequently used reaction which is related conceptually and mechanistically to the transformations reviewed here is the acyloin condensation. This method couples esters or achieves the cyclization of diesters to α -hydroxyketones by a dissolving metal reduction. It is now usually carried out in the presence of trimethylsilyl chloride to trap the intermediate enediolate dianion. Two recent reviews cover this reaction in depth.³²

Magnesium, aluminum and zinc amalgams have been employed in the reduction of ketones and aldehydes to vicinal diols,³³ and pinacols are sometimes side products in Clemmenson reductions.¹⁰ Corey and Carney performed the pinacol reduction in the presence of dimethyldichlorosilane, which increased the yield by minimizing the extent of side reactions, such as the aldol condensation. Electrochemical reductive coupling is sometimes a useful method for the preparation of glycols,^{35,18} but yields are often low, and α,β -unsaturated carbonyl compounds frequently couple at the β -carbon atoms.

V. Mechanism. In spite of the diversity of the transition metal reagents described above, the mechanistic pathways which have been proposed to account for

the transformations are similar enough to warrant their being treated under a single heading.

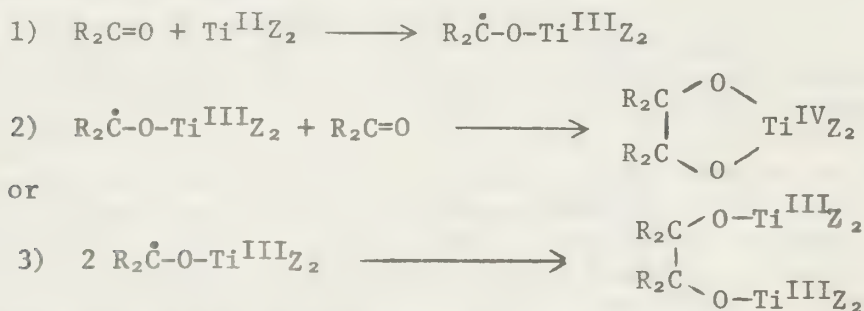
The details of the mechanisms have not been worked out, and indeed they cannot be until the inorganic reagents and inorganic products have been characterized more fully. With the exceptions of McMurry's titanium trichloride/alkali metal reagent (which is clearly the free metal) and one of Sharpless' reagents (K_2WCl_6), even the oxidation state of the metal in the reagents has not been unambiguously determined. McMurry claims that his reagent contains titanium (II) because it is black,¹¹ but one of Corey's titanium (II) reagents is described as yellow-green.^{7a} A well characterized titanium (II) species ($TiCl_2 \cdot 2AlCl_3 \cdot \text{hexamethylbenzene}$) and the titanium (III) species, cyclopentadienyl titanium dichloride, both reduce carbonyl compounds to pinacols.^{7a,21}

Ashby and co-workers³⁶ have found that at low temperatures, McMurry's $TiCl_3/LiAlH_4$ reagent can effect the 1,4-reduction of α,β -unsaturated ketones without coupling, a transformation that they were also able to carry out with AlH_2Cl or $AlHCl_2$. Evidently, two different reducing agents are produced in the reaction of lithium aluminum hydride with titanium trichloride, perhaps a mixed aluminum hydride which is thermally unstable and a low-valent titanium species which effects coupling only at elevated temperatures.

The inorganic product of the titanium-mediated reactions is sometimes assumed to be titanium dioxide.^{4a,7}

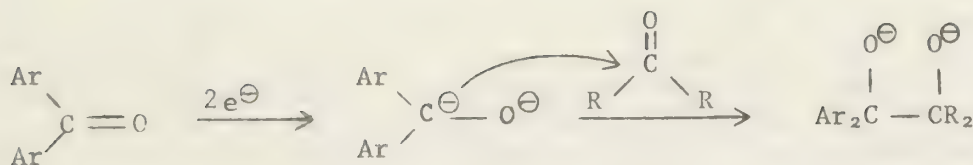
One point which has been fairly clearly established is that the coupling of carbonyl compounds to olefins proceeds via pinacols. If the reaction is interrupted^{3,11} or performed at lower temperatures,^{7a,9} pinacols can be isolated instead of or in addition to the olefins.

The mechanistic pathways that have been proposed for the pinacol coupling reaction with the transition metal reagents are analogous to those suggested for the metal- or electrolysis-induced reductions.³² It seems likely that a ketyl radical-anion or O-metallated radical is first formed by one-electron transfer from the reduced metal species. This radical then attacks another molecule of ketone or couples with another radical to produce the dianion of a pinacol or a di-O-metallated pinacol. This sequence was well summarized for the titanium (II) reagents by Corey^{7a} (Z is an unspecified ligand--Cp or halogen):



That the pinacol is produced in a deprotonated form is clear, since hydrolysis is necessary during workup.⁵

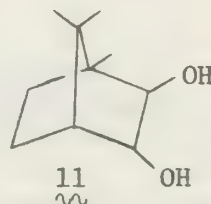
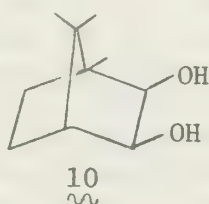
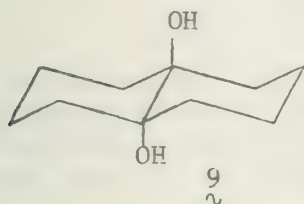
McMurry²³ has hypothesized, on the basis of reduction potentials,³⁷ that the crossed pinacol coupling of diaryl ketones with dialkyl ketones proceeds via the attack of a diaryl dianion on an unreduced ketone:



The deoxygenation of pinacols is generally thought to proceed via the loss of metal oxide from a 5-membered cyclic intermediate:



The intermediacy of the cyclic metal oxide is consistent with the fact that the olefin isomer obtained is primarily that which would be expected from a syn-elimination of the two hydroxyl groups. In the tungsten-mediated deoxygenations the percentage of the unexpected isomer in the product is approximately equal to the amount of epimerization which occurs in the recovered starting material, suggesting that the isomerization occurs before the elimination.³⁸ It has also been found that the reductive elimination proceeds only for those compounds in which the two hydroxyl groups can be oriented gauche or eclipsed to one another. As mentioned above, the reaction fails with the vicinal diaxial diol, trans-decalin-9,10-diol (9), although the diols 10 and 11 are reduced at the same rate.³⁹



The product olefin is apparently not bound covalently to nor complexed strongly with the metal, since it can be isolated without the necessity of a hydrolysis step during work-up.

VI. Summary. Some representative results for the carbonyl to olefin coupling reaction are shown in Table 1:

Table 1: Direct Reduction of Carbonyl Compounds to Olefins

Carbonyl Compound	Reagent	Conditions	% Yield	Ref.
acetophenone	1.9WCl ₆ /3.9BuLi	25 C, 6hr, THF	44%	2
benzophenone	0.5TiCl ₃ ·3THF/1.25Mg	40 C, Ar atm., THF	67%	5
benzophenone	1.5TiCl ₃ /3Zn	THF reflux, 5hr, Ar	97%	9
benzophenone	2TiCl ₃ /1LiAlH ₄	THF reflux, 4hr, N ₂	95%	11
2-butanone	3.6WCl ₆ /7.2BuLi	25 C, THF	10%	2
acetaldehyde	0.5TiCl ₃ ·3THF/1.25Mg	40 C, Ar, THF	60%	5
cycloheptanone	2TiCl ₃ /1LiAlH ₄	THF reflux, N ₂	85%	11
di-isopropyl ketone	4TiCl ₃ /13K	THF reflux, N ₂	40%	19
cycloheptanone	4TiCl ₃ /13K	THF reflux, N ₂	86%	19

From these data it can be seen that both McMurry's $\text{TiCl}_3/\text{LiAlH}_4$ reagent and Mukaiyama's TiCl_4/Zn reagent are preparatively useful for the coupling of aromatic ketones. For the olefination of aliphatic ketones, McMurry's $\text{TiCl}_3/\text{LiAlH}_4$ and $\text{TiCl}_3/\text{alkali metal}$ reagents give the best yields. The TiCl_3/Li combination is the only method which has been utilized in the cross coupling reaction.

Table 2 shows some representative results for the reductive coupling of carbonyl compounds to 1,2-diols:

Table 2: Reduction of Carbonyl Compounds to Vicinal Diols

Carbonyl Compound	Reagent	Conditions	% Yield	Ref.
Acetophenone	$1.5\text{TiCl}_4/3\text{Zn}$	20 C, 2hr, Ar	91%	9
benzaldehyde	$1.5\text{TiCl}_4/3\text{Mg(Hg)}$	0 C, Ar	84%	7a
benzaldehyde	$\text{Cr(ClO}_4)_2$	25 C, 3 days, EtOH(aq)	69%	25
benzophenone	$1\text{Mg}/1\text{MgI}_2$		99.6%	27
acetophenone	Al(Hg)	EtOH/benzene reflux	53-59%	33a
benzaldehyde	e^-	Pt cathode, $\text{KHSO}_4(\text{aq})$	50-65%	35b
cyclohexanone	$0.5\text{TiCl}_3 \cdot 3\text{THF}/1.25\text{Mg}$	40 C, Ar	45%	5
cyclohexanone	$1.5\text{TiCl}_4/3\text{Mg(Hg)}$	0 C, 30 min, Ar	93%	7a
acetone	e^-	Zn cathode, high pH	50-60%	35b

The reagents of choice for the reduction of aromatic compounds are Mukaiyama's TiCl_4/Zn and Corey's $\text{TiCl}_4/\text{Mg(Hg)}$ reagents, although Gomberg and Bachmann's method or the photochemical reduction may prove superior for diaryl ketones. Corey's $\text{CpTiCl}_2/\text{LiAlH}_4$ reagent seems to be the best available for pinacol cyclizations.

Glycols are best deoxygenated with McMurry's $\text{TiCl}_3/\text{alkali metal}$ reagent, as this produces the olefin in better yields than does Sharpless' tungsten reagent.

In general, the new titanium reagents provide simple methods for the synthesis of otherwise difficultly accessible olefins and for the preparation of vicinal diols obtainable only in lower yields by other methods.

BIBLIOGRAPHY

1. K. B. Sharpless and T. Flood, J. Chem. Soc. Chem. Commun., 370 (1972).
2. K. B. Sharpless, M. Umbreit, M. Nieh, and T. Flood, J. Am. Chem. Soc., 94, 6538 (1972).
3. M. Umbreit and E. H. White, J. Org. Chem., 41, 480 (1976).
4. (a) E. E. van Tamelen and M. Schwartz, J. Am. Chem. Soc., 87, 3277 (1965); (b) K. B. Sharpless, R. Hanzlik and E. E. van Tamelen, J. Am. Chem. Soc., 90, 209 (1968).
5. S. Tyrlik and I. Wolochowicz, Bull Soc. Chim. Fr., 2147 (1973).
6. E. E. van Tamelen and D. Seeley, J. Am. Chem. Soc., 91, 5194 (1969) and references cited therein.

7. (a) E. J. Corey, R. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, 41, 260 (1976); (b) E. J. Corey, J. F. Arnett and G. Widiger, *J. Am. Chem. Soc.*, 97, 430 (1975).
8. See also (a) D. Botteron and G. Wood, *J. Org. Chem.*, 30, 3871 (1965); (b) J. M. Conia and M. J. Bobson, *Angew. Chem. Int. Ed. Engl.*, 14, 473 (1975); (c) J. Barnier, J. Denis, J. Salaun and J. M. Conia, *Tetrahedron*, 30, 1397 (1974) and references cited therein.
9. T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Lett.*, 1041 (1973).
10. M. Minabe, M. Yoshida, M. Fujimoto, and K. Suzuki, *J. Org. Chem.*, 41, 1935 (1976).
11. (a) J. E. McMurry and M. Fleming, *J. Am. Chem. Soc.*, 96, 4708 (1974); (b) J. E. McMurry, *Acc. Chem. Research*, 7, 281 (1974).
12. H. Wynberg, K. Lammertsma, and L. Hulshof, *Tetrahedron Lett.*, 3749 (1975).
13. R. F. Langler and T. Tidwell, *Tetrahedron Lett.*, 777 (1975).
14. D. Bomse and T. Morton, *Tetrahedron Lett.*, 781 (1975).
15. G. A. Olah, G. S. Prakash, and G. Liang, *Synthesis*, 319 (1976).
16. A. L. Baumstark, E. Bechara, and M. Semigran, *Tetrahedron Lett.*, 3265 (1976).
17. L. Barlow and G. Pattenden, *J. Chem. Soc., Perkin I*, 1029 (1976).
18. L. A. Paquette, I. Itoh, and W. Farnham, *J. Am. Chem. Soc.*, 97, 7280 (1975).
19. J. E. McMurry and M. Fleming, *J. Org. Chem.*, 41, 896 (1976).
20. J. E. McMurry and M. Silvestri, *J. Org. Chem.*, 40, 2687 (1975).
21. R. S. P. Coutts, P. C. Wailes, and R. L. Martin, *J. Organometal. Chem.*, 50, 145 (1973).
22. R. D. Rieke and P. M. Hudnall, *J. Am. Chem. Soc.*, 94, 7178 (1972).
23. J. E. McMurry and L. Krepski, in press.
24. J. B. Conant and H. B. Cutter, *J. Am. Chem. Soc.*, 48, 1016 (1926).
25. D. D. Davis and W. B. Bigelow, *J. Am. Chem. Soc.*, 92, 5127 (1970).
26. G. W. Griffin and R. B. Hager, *J. Org. Chem.*, 28, 599 (1963).
27. M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, 49, 236 (1927).
28. (a) G. Ciamician and P. Silber, *Chem. Ber.*, 33, 2911 (1900); (b) W. D. Cohen, *Rec. Trav. Chim. Pays-Bas*, 39, 243 (1920).
29. L. F. Fieser, "Organic Experiments", 2nd ed., Raytheon, Lexington, Mass., 1968, pp. 205-207.
30. (a) A. Schönberg, "Preparative Organic Photochemistry", Springer Verlag, Berlin, 1968, pp. 203-213; (b) R. O. Kan, "Organic Photochemistry", McGraw-Hill, New York, 1966, pp. 222-224.
31. G. Porter and P. Suppan, *Trans. Faraday Soc.*, 61, 1664 (1965).
32. (a) J. J. Jordan, D. C. Owsley, and J. M. Nelke, *Organic Reactions*, 23, 259 (1976); (b) K. Rühlmann, *Synthesis*, 236 (1971); (c) see also H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, Calif., 1972, pp. 169-172.
33. (a) M. S. Newman, *J. Org. Chem.*, 26, 582 (1961); (b) A. Vigevani, R. Pasqualucci, G. Gallo, and G. Pifferi, *Tetrahedron*, 25, 573 (1969) see also ref. 8a and ref. 32c, p. 168.
34. E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.*, 93, 7318 (1971).
35. (a) R. E. Sioda, B. Terem, J. H. P. Utley, and B. C. L. Weedon, *J. Chem. Soc., Perkin I*, 561 (1976); (b) M. M. Blaizer, "Organic Electrochemistry", Marcel Dekker, New York, 1973, chapters XVIII and IX.
36. (a) E. C. Ashby and J. J. Linn, *Tetrahedron Lett.*, 4453 (1975); (b) E. C. Ashby, J. J. Linn, and R. Kovar, *J. Org. Chem.*, 41, 1939 (1976).
37. L. Meites, "Polarographic Techniques", Interscience Publishers, New York, 1965, pp. 671, ff.
38. For similar cases see (a) M. Schlosser and P. Weiss, *Synthesis*, 257 (1970) and (b) A. Collet, *Synthesis*, 664 (1973).
39. J. E. McMurry, personal communication.

ORGANOSILICON REAGENTS IN CARBON-CARBON BOND FORMATION

Reported by Craig Kubitschek

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The trialkylsilyl group has become an increasingly important functional group in organic synthesis. Because of its low electronegativity, silicon forms relatively weak bonds to less electronegative and relatively strong bonds to more electronegative elements (Table 1).

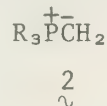
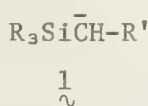
Table 1. Bond Strengths of Representative Compounds¹

C-H	104 kcal/mole	Si-H	94
C-C	88	Si-C	77
C-O	92	Si-O	111
C-Cl	84	Si-Cl	88

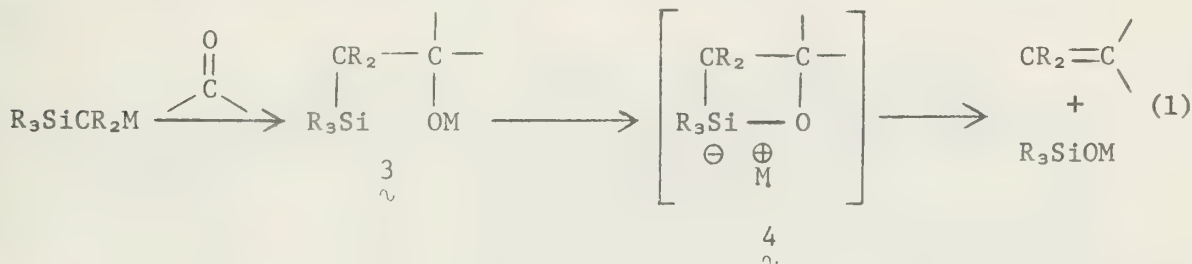
Thus, silicon is easily removed from organic molecules; for example, it is thermodynamically favorable to break a Si-C bond and form a Si-O bond. The presence of a β-trialkylsilyl group appears to stabilize carbonium ions, an effect which may be due either to induction or hyperconjugation. Silicon is able to stabilize adjacent carbanions as well,² and is fairly susceptible to nucleophilic attack. d-Orbital participation has been invoked to explain both of these properties: silicon's vacant d orbitals could reasonably stabilize a carbanion by overlap with the filled p orbitals, and could allow formation of a pentacoordinate intermediate during nucleophilic substitution.

Historically, trialkylsilyl groups have been used to render high-boiling compounds more volatile for use in gas chromatography and mass spectroscopy.³ They have also served as protecting, blocking, and activating groups, generally when attached to various heteroatoms.⁴ Recently, progress has been made in synthetic reactions involving reagents with C-Si bonds. The use of such organosilicon compounds in forming new C-C bonds constitutes the subject of this seminar.

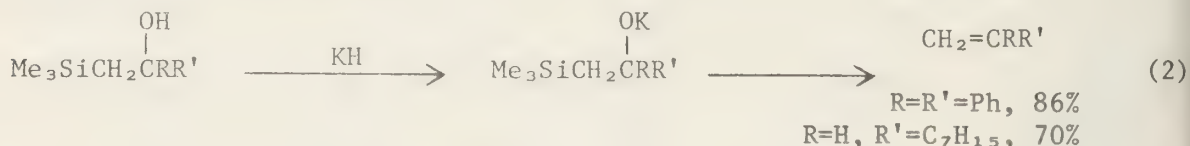
The Peterson Reaction. One of the most influential pieces of work in this area is the reaction of α-trialkylsilyl carbanions with carbonyl compounds to form olefins, a process devised by Peterson to complement the well-known Wittig reaction. Peterson reasoned that α-trialkylsilyl carbanions (1) could take the place of the phosphorus ylide (2), since both silicon and phosphorus are readily attacked by alkoxides and both have d orbitals which may enter into pentavalent bond formation.⁵



Thus, a reaction such as Eq. 1 could be envisioned.



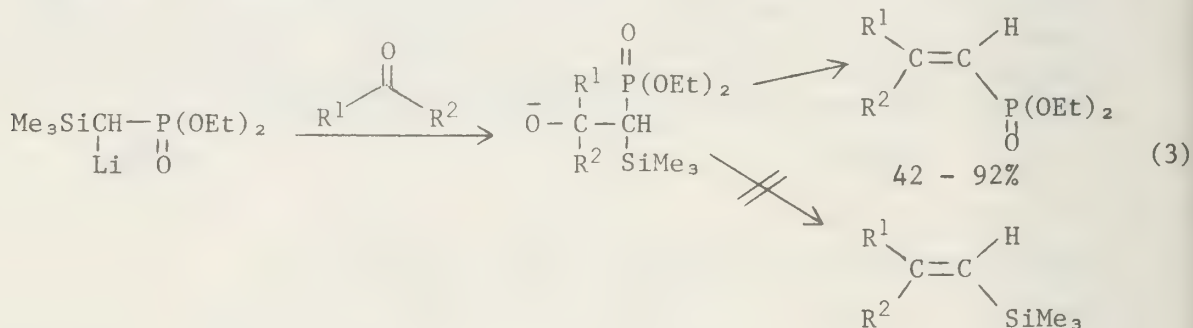
Peterson therefore prepared four β -silylcarbinols from trimethylsilylmethylmagnesium chloride and the appropriate carbonyl compounds; when the β -silylcarbinols were treated with sodium hydride or potassium hydride in tetrahydrofuran, the salts formed underwent elimination to form the desired olefins in good yield. The elimination also proceeded smoothly in the presence of a catalytic amount of sulfuric acid.



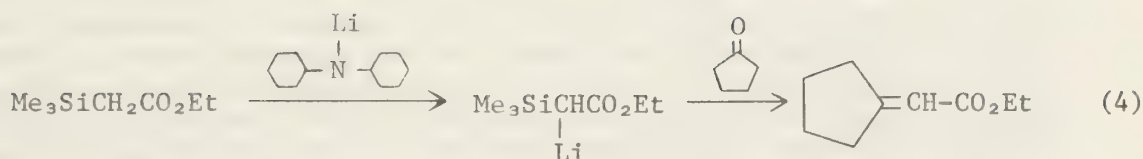
Since only a limited number of alkylsilyl Grignard reagents were available, a different method of forming the α -silyl organometallic reagents was sought. Peterson found that *n*-butyllithium effected quantitative metallation at the α -position of silanes having the form (CH₃)₃SiCH₂R (R = Ph₂P-, CH₃S-, C₆H₅-). The metallated silanes will undergo reaction with carbonyl compounds to give the desired olefins.

The Peterson reaction, as it is now often called, has received considerable attention since Peterson's first report. A number of routes to the silanes exist (for example, Peterson⁵ prepared (trimethylsilylmethyl)diphenylphosphine; Carey⁶ has synthesized trimethylsilyl-1,3-dithiane through the reaction of 2-lithio-1,3-dithiane with trimethylsilyl chloride.) Chan and coworkers⁷ have reported several methods which increase the generality of the reaction. Among these are another method of carbanion formation (that of addition of organolithium compounds to a vinylsilane), use of a more active metallating agent (*n*-butyllithium/TMEDA), a more satisfactory method of methylenation (reaction of the intermediate β -carbinol with thionyl chloride to effect β -elimination), and the synthesis of allenes and cyclopropenes.

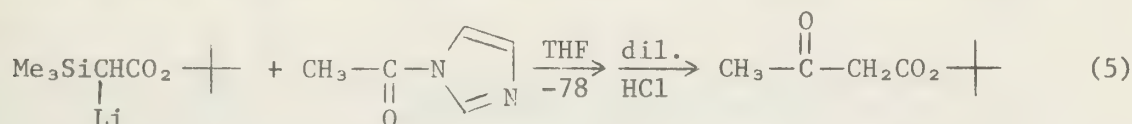
Carey and Court⁸ found that the reaction was applicable to the synthesis of various heteroatom-substituted olefins, including vinyl phosphonates and vinyl sulfoxides. Their results with diethyl 1-lithiotrimethylsilylphosphonate are particularly interesting, as they show that the elimination of siloxide is favored over the elimination of phosphate.



Yamamoto, Nozaki, and coworkers⁹ have reported a synthesis of α,β -unsaturated esters with ethyl lithiotrimethylsilylacetate as the nucleophile. The authors note that this method has advantages over the Wittig-type reactions in several cases; chalcone, which often gives a mixture of products in low yields, in this case gave an 86% yield, while cyclopentanone, which often undergoes enolate condensation reactions after proton transfer, reacted smoothly according to Eq. 4.

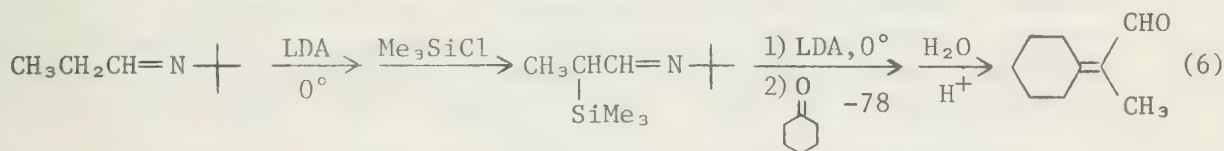


Rathke¹⁰ has developed a similar method, using instead the *tert*-butyl ester of lithiotrimethylsilylacetate and lithium diisopropylamide (LDA). Yields of 92-98% with seven different carbonyl compounds have been reported. This method is reported to give better yields under milder conditions than does the Emmons-Wadsworth; the authors attribute this improvement to the greater reactivity of the lithium enolate, compared to that of the phosphorus ylide. It also gives cleaner products; when cyclohexanone reacts with the diethylphosphonate ylide of ethyl acetate to form ethyl cyclohexylideneacetate, the non-conjugated product is formed in 6% yield. Hartzell and coworkers found only .4% of the non-conjugated product with their method. *t*-Butyl lithiotrimethylsilylacetate also reacts with acyl imidazoles to form β -ketoesters in good (50-94%) yields,¹¹ as Rathke has demonstrated (Eq. 5).

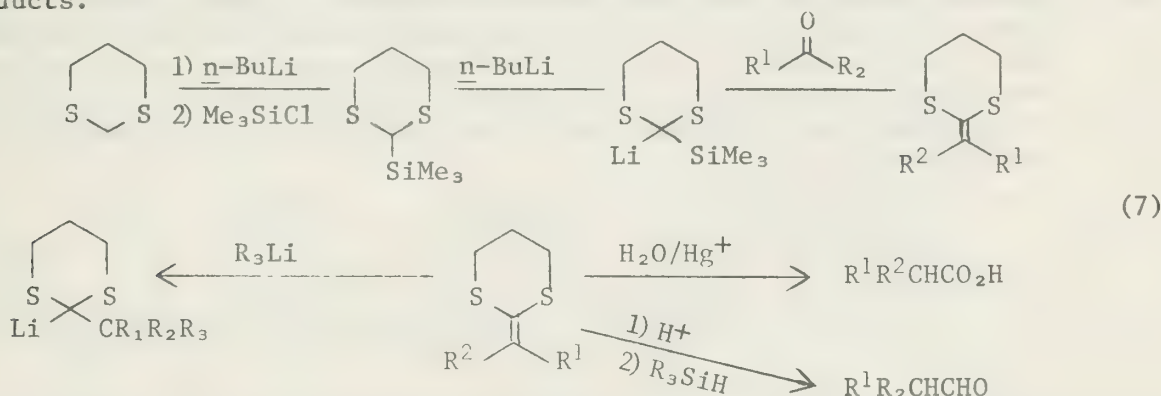


Ojima has synthesized α,β -unsaturated nitriles by a similar method.¹²

Corey has developed an elegant synthesis of unsaturated aldehydes, in which α -silyl aldehyde *t*-butylimines serve as enolates.¹³

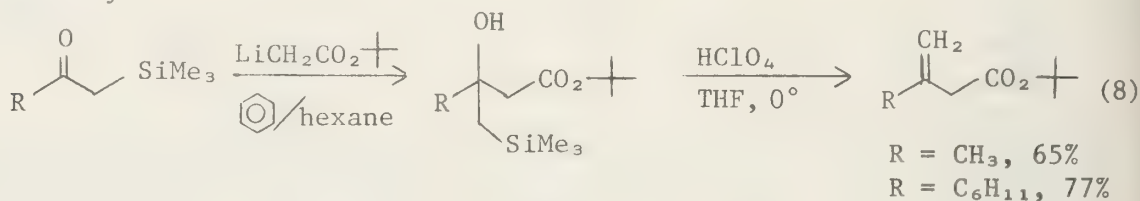


Of the numerous variations on the parent reaction that have appeared recently, one of the most synthetically useful is the ketene thioacetal synthesis¹⁴ discovered independently by Seebach, Jones, and Carey. The following four-step reaction sequence (Eq. 7) affords the ketene thioacetals, which can subsequently undergo transformations to a variety of organic products.

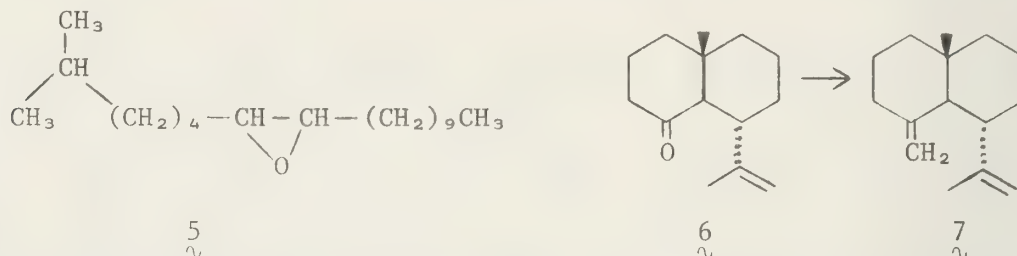


In an interesting modification, Hudrlik has synthesized olefins from β -ketosilanes.¹⁵ β -Ketosilanes can be prepared by the reaction of a silyl

Grignard with an anhydride¹⁶ or the reaction of a silyllithium reagent with an aldehyde or carboxylic acid.¹⁵ Organometallic reagents will add to these ketones; the alcohols thus formed then undergo β -elimination readily to yield olefins. In this approach, both parts of the leaving group, *i.e.* the trialkylsilyl and oxygen moieties, are derived from the original molecule, rather than from two different sources. Ruden and Gaffney¹⁷ have used this method to synthesize β,γ -unsaturated esters, amides, and nitriles regio-specifically.

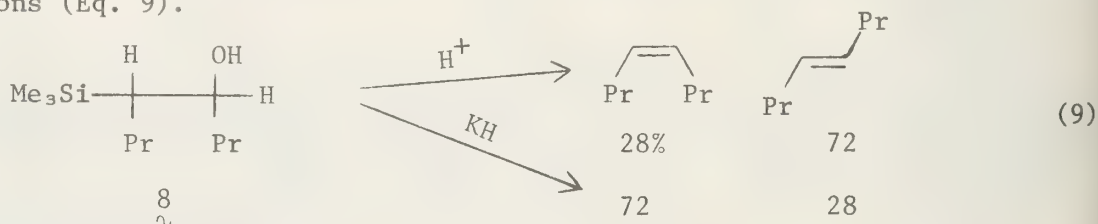


The Peterson reaction has already found applications in natural product synthesis. Chan^{7b} has used it in a simple synthesis of the gypsy moth sex pheromone **5**, as has Boeckman¹⁹ in his total synthesis of gorgonene (**7**).



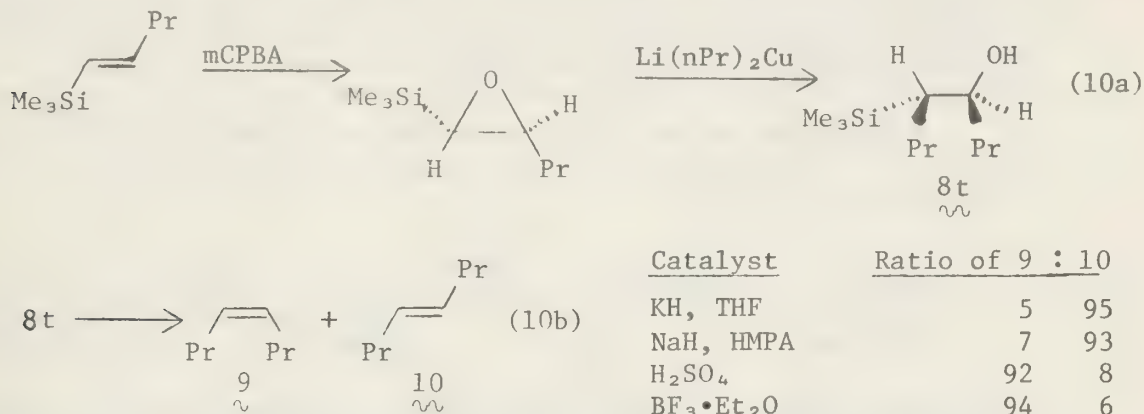
The methylenation of ketone **6** with methylenetriphenylphosphorane was unsuccessful. When methyllithium was added to the starting ketone to produce the tertiary carbinol, subsequent dehydration gave complex mixtures of olefinic products. However, addition of trimethylsilylmethylmagnesium chloride followed by elimination in 3:1 acetic acid/water gave the olefin in 15% yield.

Mechanism of the Reaction and Related Synthetic Implications. Early workers in the area assumed that the elimination step in the Peterson reaction proceeded through a four-membered siloxane intermediate (**4**). However, molecular orbital calculations by Carey and Trindle¹⁸ suggested that the four-membered intermediate did not have finite existence, but was merely a transition state. The overall reaction did not appear to be stereoselective, as most reactions that could give geometrical isomers gave mixtures of the *cis*- and *trans*- products in varying proportions.^{5,7} The first stereoselective olefin synthesis with the Peterson reaction was devised by Hudrlik,²⁰ who found that the ratio of *cis*- and *trans*- isomers from the β -elimination of silanol from 5-trimethylsilyl-4-octanol (**8**) depended on the reaction conditions (Eq. 9).

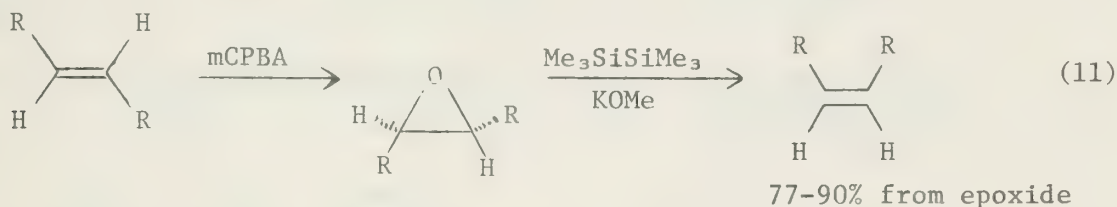


Hudrlik reasoned that the elimination reactions must therefore be stereoselective and that consequently the isomer ratio is determined by the ratio of the diastereomeric alcohols. He therefore synthesized the pure threo-

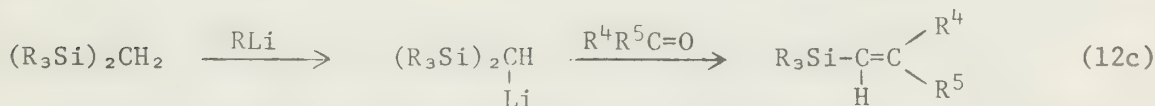
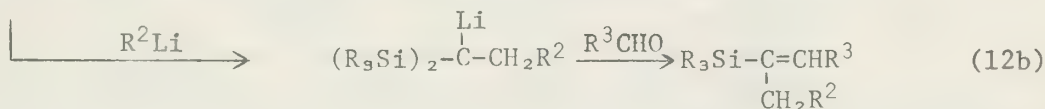
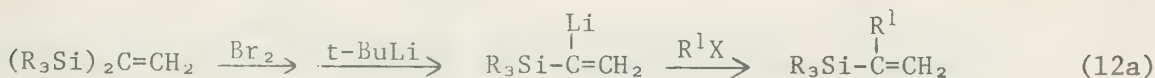
alcohol by reduction of 5-trimethylsilyl-4-octanone, and found that either stereoisomer (9,10) could be produced in good stereochemical purity by proper choice of reaction conditions. Evidently, the base-catalyzed reaction does involve a syn elimination, while the acid-catalyzed elimination is anti. Hudrlik has reported a regio- and stereoselective synthesis of β -hydroxy-alkylsilanes, which, coupled with the stereoselective eliminations, provides a general and highly stereoselective olefin synthesis.



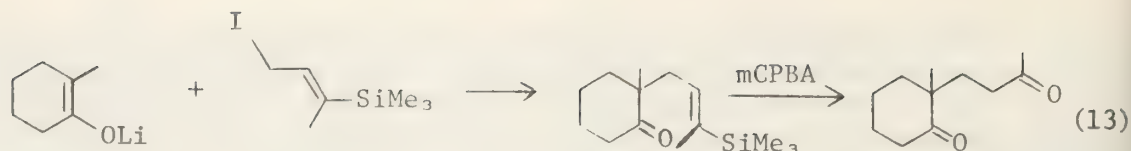
Two groups²¹ have recently reported epoxide deoxygenation reactions with aryldialkylsilyllithium and trialkylsilylpotassium. These reactions, involving backside attack of the silyl anion, followed by ring opening, rotation, and frontside elimination of the silanol, invert the stereochemistry of the epoxide. Since the epoxide itself can be formed stereospecifically from a parent olefin, this procedure represents a useful olefin inversion method.



Vinyl Silanes and Conjugate Additions. Vinyl silanes can be prepared by a number of methods, including hydrosilylation of an alkyne²² and reaction of trimethylsilyl chloride with a Grignard reagent.²³ Recently, Seebach has developed a series of syntheses from which a wide variety of substituted silanes can be made.²⁴ (Eqs. 12)

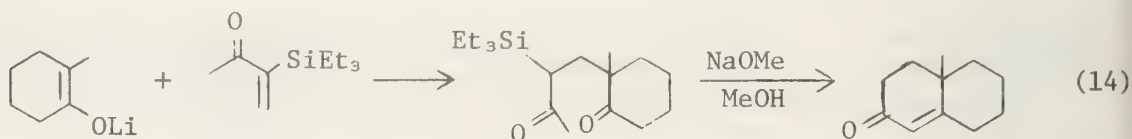


Stork²⁵ has shown that vinylsilanes can be used as carbonyl precursors via the corresponding silyl epoxides (Eq. 13).

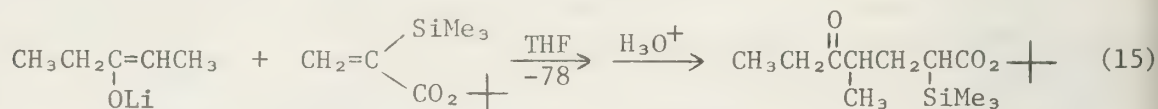


In this case, the epoxide is apparently opened by the action of the *m*-chlorobenzoic acid formed in the previous step; Stork has suggested that participation by the annular ketone accelerates this reaction. Boeckman, in a similar fashion, has demonstrated that vinylsilane carbanions are the equivalents of acyl carbanions and methyl ketone enolates.²⁶

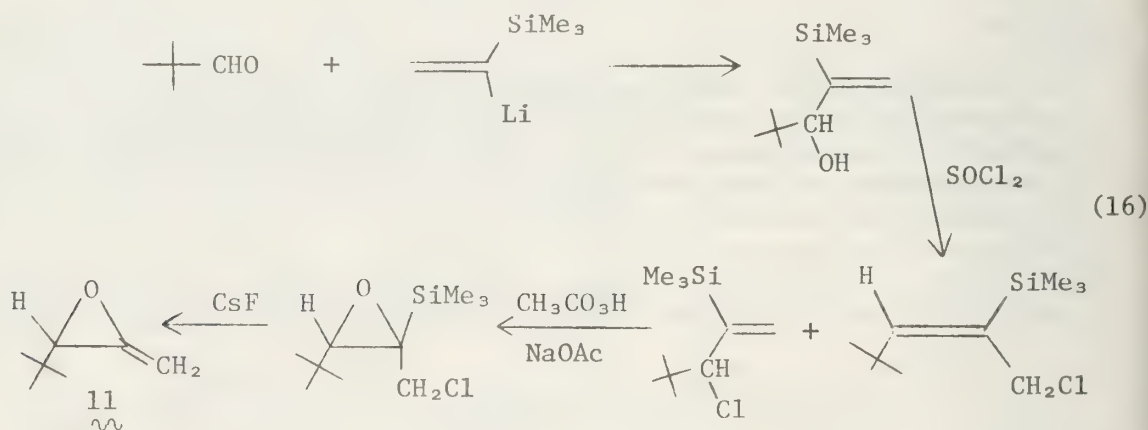
α -Silylated enones can participate in Michael addition to lithium enolates.²⁷ Conjugate addition to methylcyclohexanone is accomplished by this method (Eq. 14).



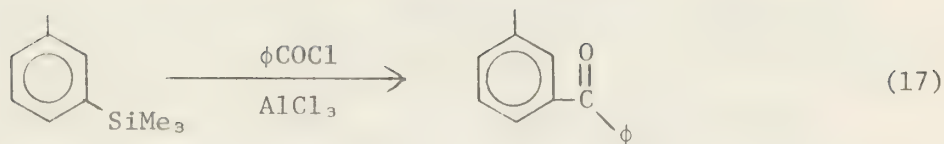
The silyl group is readily removed from the product, and cyclization to the octalone occurs in good yield under basic conditions. Boeckman and Stork²⁸ have developed a bis-annulation reagent that allows the addition of two rings at a time and have used it in the syntheses of natural products such as dl-progesterone and dl-testosterone. α -Silyl vinyl esters, which have been made via the Peterson reaction by Hartzell and Rathke,²⁹ also undergo Michael addition with lithium enolates (Eq. 15).



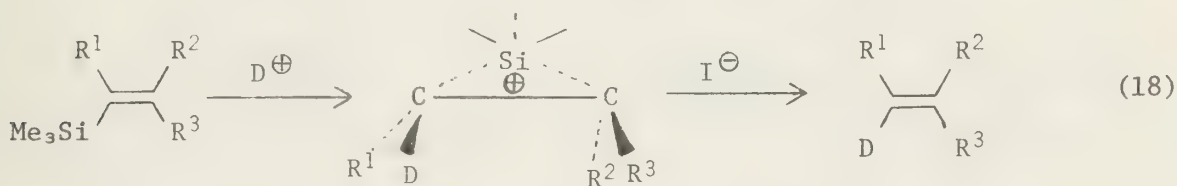
Chan³⁰ has recently synthesized the highly strained allene oxide (11) by a similar route.



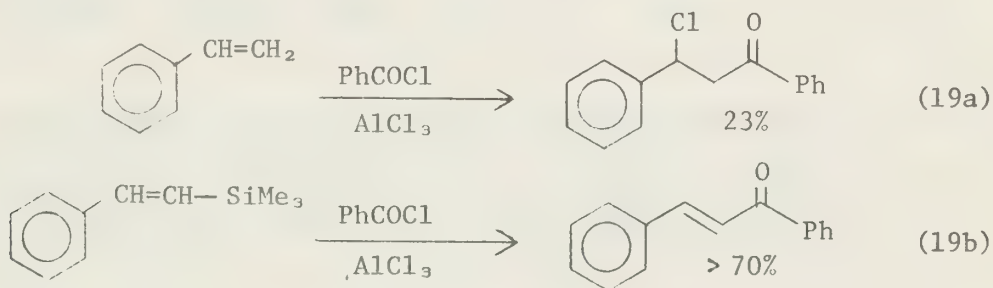
Stabilization of Carbonium Ions by Silicon-Carbon Bonds. In addition to providing stabilization for α -carbanions, silicon can stabilize β -carbonium ions. This property has seen considerable application in aromatic substitution reactions.³¹ Substituted aryl silanes usually undergo electrophilic substitution at the silyl group, despite the presence of other directing groups (Eq. 17).



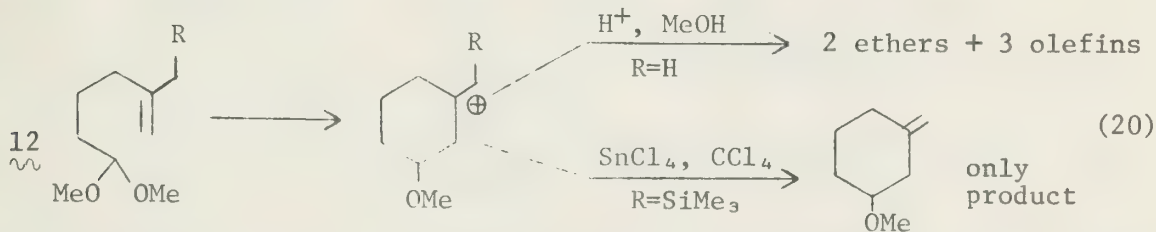
Silicon has also been implicated in bridging or hyperconjugative stabilization of β -trialkylsilyl carbonium ions,³² a stabilization demonstrated by the stereospecific reactions of vinylsilanes with bromine and hydrogen iodide. The latter reaction therefore presents a stereoselective method for deuteration of olefins (Eq. 18).



Recently, Fleming and coworkers have made use of the ability of the C-Si bond to stabilize adjacent carbonium ions in aliphatic Friedel-Crafts reactions. A directing group is particularly important in these reactions, as carbonium ion reactions are notorious for giving mixtures of products or rearranged products (Eqs. 19).



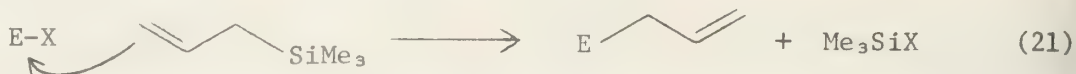
Further work by Fleming³⁴ which demonstrates the utility of silicon in directing the course of a reaction involves the unsaturated acetal 12 (Eq. 20).



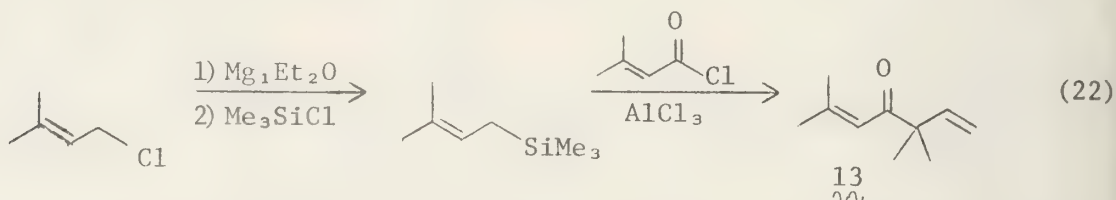
Although the conclusion is not definite, since the two reactions were run under different conditions, it appears that silicon controls product formation from the intermediate carbonium ion much better than does hydrogen.

Alkynyl silanes have also been used in Friedel-Crafts reactions, as is shown by Newman's procedure for the synthesis of unsaturated aldehydes³⁵ and Calas' method for producing unsaturated alcohols.³⁶

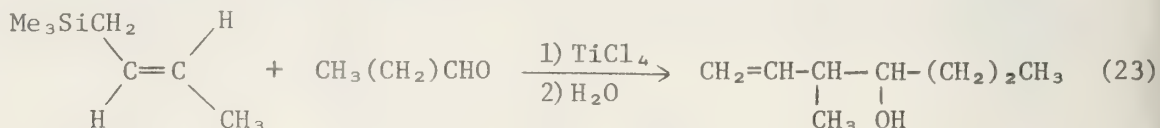
Allyl Silanes. Allyl silanes, readily available from Grignard reactions of the corresponding chlorides,²³ appear to react with a variety of electrophiles (E-X) in the manner shown in Eq. 21.



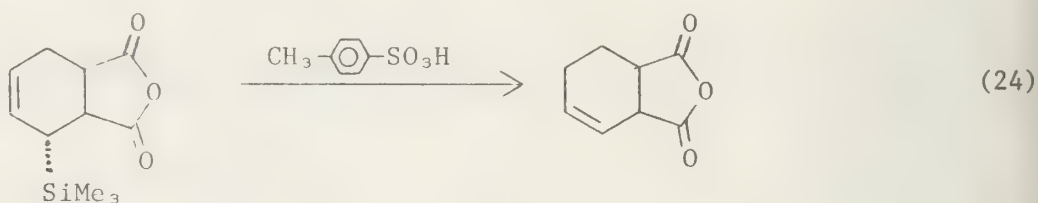
Considerable interest has been displayed in the reaction of these compounds in recent months. Calas and coworkers³⁷ have synthesized a number of γ,δ -unsaturated alcohols, from allylsilanes and aldehydes. They have also reported a new and superior method for the synthesis of the monoterpenoid ketone 13 via the acid-catalyzed reaction of an allylsilane with the appropriate acid chloride.



Sakurai and Hosomi³⁸ have independently developed a synthesis of γ,δ -unsaturated alcohols, and shown its generality by applying the method to the synthesis of eighteen different alcohols in yields of 44-91% (Eq. 23).



In addition, Fleming and Carter³⁹ have used the "protodesilylation reaction" to modify the structure of the anhydride formed by the Diels-Alder reaction of maleic anhydride and 1-trimethylsilylbutadiene. The ability to shift the position of the double bond in a Diels-Alder adduct will undoubtedly be of considerable utility in synthesis.



BIBLIOGRAPHY

1. (a) "CRC Handbook of Chemistry and Physics," 51st edition; (b) C. H. Van Dyke, "Organometallic Compounds of the Group IV Elements," Vol. 1, A. G. McDiarmid, ed., M. Dekker, New York, 1968.
2. M. F. Lappert and R. Pierce, JCS Chem. Comm., 24 (1973).
3. A. E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Co., Rockford, Illinois, 1968.
4. J. F. Klebe, Advances Org. Chem., 8, 98, (1972).
5. D. J. Peterson, J. Org. Chem., 33, 780 (1968).
6. F. A. Carey and A. S. Court, J. Org. Chem., 37, 939 (1972).

7. (a) T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Lett.*, 1137 (1970); (b) T. H. Chan and E. Chang, *J. Org. Chem.*, 39, 3264 (1974); (c) T. H. Chan and D. Massuda, *Tetrahedron Lett.*, 3383 (1975); (d) T. H. Chan and W. Mychajlowskij, *Tetrahedron Lett.*, 171 (1974).
8. (a) F. A. Carey and A. S. Court, *J. Org. Chem.*, 37, 939 (1972); (b) F. A. Carey and O. Hernandez, *J. Org. Chem.*, 38, 2670 (1973).
9. (a) K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, 96, 1620 (1974); (b) H. Taguchi, K. Shimoji, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Japan*, 47, 2529 (1974).
10. S. L. Hartzell, D. F. Sullivan, and M. W. Rathke, *Tetrahedron Lett.*, 1403 (1974).
11. S. L. Hartzell, and M. W. Rathke, *Tetrahedron Lett.*, 2757 (1976).
12. I. Ojima and M. Kumagi, *Tetrahedron Lett.*, 4005 (1974).
13. E. J. Corey, D. Enders, and M. G. Bock, *Tetrahedron Lett.*, 7 (1976).
14. (a) B.-T. Gröbel and D. Seebach, *Angew. Chem. Int. Ed. Eng.*, 13, 83 (1974); (b) D. Seebach, M. Kolb, and B.-T. Gröbel, *Chem. Ber.*, 106, 2277 (1973); (c) P. F. Jones and M. F. Lappert, *JCS Chem. Comm.*, 526 (1972); (d) P. F. Jones, M. F. Lappert, and A. C. Szary, *JCS Perkin I*, 2272 (1973).
15. P. F. Hudrlik and D. Peterson, *Tetrahedron Lett.*, 1758 (1972).
16. C. R. Hauser and C. R. Hance, *J. Am. Chem. Soc.*, 74, 5091 (1952).
17. R. A. Ruden and B. L. Gaffney, *Synthetic Comm.*, 5, 15 (1975).
18. C. Trindle, J.-T. Hwang, and F. A. Carey, *J. Org. Chem.*, 38, 2264 (1973).
19. R. K. Boeckman and S. M. Silver, *J. Org. Chem.*, 40, 1755 (1975).
20. (a) P. F. Hudrlik and D. Peterson, *Tetrahedron Lett.*, 1133 (1974); (b) P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, 97, 1464 (1975); (c) P. F. Hudrlik, D. Peterson, and J. Rona, *J. Org. Chem.*, 40, 2263 (1975).
21. (a) M. T. Reetz and D. Plachky, *Synthesis*, 199 (1976); (b) P. B. Dervan and M. A. Shipley, *J. Am. Chem. Soc.*, 98, 1265 (1976).
22. C. Eaborn and R. W. Bott, "Organometallic Compounds of the Group IV Elements," Vol. 1, A. G. McDiarmid, ed., M. Dekker, New York, 1968, and references therein.
23. H. Sakurai, A. Hosomi, M. Kumada, *J. Org. Chem.*, 34, 1764 (1969).
24. D. Seebach, B. T. Gröbel, A. K. Beck, M. Braun, and K. H. Geiss, *Ang. Chem. Int. Ed. Eng.*, II, 443 (1972).
25. (a) G. Stork and E. Colvin, *J. Am. Chem. Soc.*, 93, 2080 (1971); (b) G. Stork and M. E. Jung, *J. Am. Chem. Soc.*, 96, 3682 (1974).
26. R. K. Boeckman and K. J. Bruza, *Tetrahedron Lett.*, 38 (1974).
27. G. Stork and B. Ganem, *J. Am. Chem. Soc.*, 95, 6152 (1973).
28. (a) R. K. Boeckman, *J. Am. Chem. Soc.*, 96, 6179 (1974); (b) G. Stork and J. Singh, *ibid.*, 96, 6181 (1974).
29. S. L. Hartzell and M. W. Rathke, *Tetrahedron Lett.*, 2737 (1976).
30. T. H. Chan, B. S. Ong, and W. Mychajlowskij, *Tetrahedron Lett.*, 3253 (1976).
31. (a) I. Fleming, *Chem. and Ind.*, 449 (1975) and references contained therein; (b) V. Chavlovsky and V. Bazant, *Collect. Czech. Chem. Commun.*, 16, 580 (1951); (c) T. Hashimoto, *J. Pharm. Soc. Japan*, 87, 528 (1967).
32. (a) K. Koenig and W. Weber, *Tetrahedron Lett.*, 2533 (1973); (b) K. Utimoto, M. Kitai, and H. Nozaki, *ibid.*, 2824 (1975).
33. I. Fleming and A. Pearce, *JCS Chem. Comm.*, 633 (1975).
34. I. Fleming, A. Pearce, and R. Snowdon, *JCS Chem. Comm.*, 182 (1976).
35. H. Newman, *J. Org. Chem.*, 38, 2254 (1973).
36. G. Deleris, J. Dunogues, and R. Calas, *Tetrahedron Lett.*, 2449 (1976).
37. J.-P. Pillot, J. Dunogues, and R. Calas, *ibid.*, 1871 (1976).
38. A. Hosomi and H. Sakurai, *ibid.*, 1295 (1976).
39. I. Fleming and M. J. Carter, *JCS Chem. Comm.*, 679 (1976).

METAL HYDRIDES AS REAGENTS FOR CONJUGATE REDUCTION

Reported by Charles Boeder

November 18, 1976

This seminar presents metal hydride reagents as possible alternatives to dissolving metals, e.g., $(\text{Li}/\text{NH}_3)^{1,2}$ for the reduction of the carbon-carbon double bond of α,β -unsaturated carbonyl compounds. Until recently, the use of hydride type reagents for this transformation has seldom been practical. Reduction products varied among the desired saturated carbonyl compounds, allylic alcohols, and unsaturated hydrocarbons.^{3,4,5} Brown showed that the reduction of cyclopentenones with lithium aluminum hydride or sodium borohydride gives varying amounts of the saturated alcohol.⁶ Sodium borohydride reduces the conjugated carbon-carbon double bond in selected enones, but the reduction is not general.⁷

Recently, lithium and potassium tri-sec-butylborohydride (L and K-Selectride from Aldrich) have been used in the reduction of various α,β -unsaturated ketones and esters.^{8,9,10} Cyclohexenones are reduced in high yield to the corresponding cyclohexanones. Selectride Reductions of enones with two substituents β to the carbonyl group afford only allylic alcohols, the 1,2 reduction product. Although Selectride reduction of acyclic α,β -unsaturated ketones also affords allylic alcohols,⁸ acyclic unsaturated esters are reduced in good yield to the saturated esters. Alkylation of the enolates resulting from 1,4 reduction of appropriate ketones and esters has also been carried out.^{9,10}

Copper hydride reagents have also been employed for conjugate hydride reduction. Reagents of the type "LiCuHR" ($\text{R} = \text{nBu}, \text{C}\equiv\text{C-nPr}, \text{SPh}, \text{O-tert-Bu}$) give high yields of saturated ketones (cyclic or acyclic) from the corresponding enones, regardless of alkyl substitution on the β -carbon.^{11,12} Thermal decomposition of lithium dialkylcuprates gives rise to copper hydride species which are responsible for saturated side products in conjugate alkylations of unsaturated carbonyl compounds.¹³ Enones and enoates are reduced to the corresponding saturated ketones and esters by simple copper hydrides generated from lithium or sodium trimethoxyaluminum hydride and cuprous bromide.¹⁴ Dihydrocuprates (MCuH_2) have been prepared but have not been reported in conjugate reductions.^{15,16}





















Special silane reagents reduce the carbon-carbon double bond in α,β -unsaturated ketones. Triethylsilane in the presence of a catalytic amount of $(\text{Ph}_3\text{P})_3\text{RhCl}$ reduces the conjugated double bond of an enone in the presence of other double bonds. Further conjugation of the enone leads to varying degrees of 1,4 and 1,2 reduction depending on the silane used.¹⁷ Prochiral olefins conjugated to the carbonyl of a ketone can be reduced asymmetrically in low optical yield when a chiral rhodium complex is used as the catalyst.¹⁸ Conjugate reduction with a triethylsilane/trifluoroacetic acid system has been reported.¹⁹

Tri-n-butyltin hydride has been used in conjugate reduction, mainly for the selective deuterium labeling of the α or β carbon of enones, enoates, or α,β -unsaturated nitriles.^{20,21}

A binuclear hydride cluster, $\text{NaHFe}_2(\text{CO})_8$, reduces the conjugated carbon-carbon bond of α,β -unsaturated ketones, esters, nitriles, amides, and lactones.²²

Finally, the reagent prepared from the reaction of lithium aluminum-hydride and cuprous iodide, H_2AlI , has been reported to give successful reductions of several acyclic ketones. β -Disubstituted enones gave high yields of the 1,4 reduction product.²³

Table 1. Representative Reductions of α,β Unsaturated Carbonyl Compounds
Compound Type (yield of 1,4 reduction)

Reducing agent	Cyclic enone	β -Disubst. enone	Acyclic enone	Acyclic enone	Octal-2-one
Selectride ^a	 (99%) ¹⁰	 (0%) ¹⁰	 (0%) ¹⁰	 (90%) ⁹	 (0%) ¹⁰
Simple $CuH^{a,14}$	 (92%)	 (98%)	 (93%) ^{b,c}	 (92%) ^b	
$CuHnBu^a$	 (95%) ¹¹	 (95%) ¹²	 (75%) ¹¹	 (47%) ¹¹	 (85%) ^{d,11}
Li/NH_3^1	 (62%)	 (84%)	 (70%)	 (18%) ^φ	 (95%) ^c

^aLi salt unless otherwise noted

^bNa salt

^creduction with LAH/CuI in 82% yield²³

^d3:3 cis:trans

^e100% trans

- Drury Caine in "Organic Reactions," Vol. 23, John Wiley and Sons, New York, New York, 1976, p. 1.
- H. O. House, "Modern Synthetic Reactions," second ed., W. A. Benjamin, Menlo Park, California, 1972.
- R. O. Hutchins and D. Kandasamy, J. Org. Chem., 40, 2530 (1975).
- M. R. Johnson and B. Rickborn, J. Org. Chem., 35, 1041 (1970).
- W. R. Jackson and A. Zurqiyah, J. Chem. Soc., 5280 (1965).
- H. C. Brown and H. M. Hess, J. Org. Chem., 34, 2206 (1969).
- J. H. Schauble, G. J. Walter, and J. G. Morin, J. Org. Chem., 39, 755 (1974) and references cited therein.
- B. Ganem, J. Org. Chem., 40, 146 (1975).
- B. Ganem and J. M. Fortunato, J. Org. Chem., 40, 2846 (1975).
- J. M. Fortunato and B. Ganem, J. Org. Chem., 41, 2194 (1976).
- R. K. Boeckman, Jr., and R. Michalak, J. Am. Chem. Soc., 96, 1623 (1974).
- S. Masamune, G. S. Bates, and P. E. Georghiou, J. Am. Chem. Soc., 96, 3686 (1974).
- H. O. House and J. C. DuBose, J. Org. Chem., 40, 788 (1975).
- M. F. Semmelhack and R. D. Stauffer, J. Org. Chem., 40, 3619 (1975).
- E. C. Ashby, T. F. Korenowski, and R. D. Schwartz, J. C. S. Chem. Commun., 157 (1974).
- T. Yoshida and E. Negishi, J. C. S. Chem. Commun., 762 (1974).
- I. Ojima and T. Nagai, Tetrahedron Lett., 5085 (1972).
- T. Hayashi, K. Yamamoto, and M. Kumada, Tetrahedron Lett., 3 (1975).
- D. N. Kursanov, N. M. Loim, V. A. Baranova, L. V. Moiseeva, L. P. Zalukaev, and Z. N. Parnes, Synthesis, 420 (1974).
- M. Pereyre, G. Colin, and J. Valade, Tetrahedron Lett., 4805 (1967).
- M. Pereyre and J. Valade, Tetrahedron Lett., 489 (1969).
- J. P. Coleman, R. G. Finke, P. L. Matlock, R. Wahren, and J. I. Brauman, J. Am. Chem. Soc., 98, 4687 (1976).
- E. C. Ashby, J. J. Lin, and R. Dovar, J. Org. Chem. 41, 1939 (1976).

RING EXPANSIONS AND CONTRACTIONS VIA CARBENES

Reported by Sharon Fradenburgh

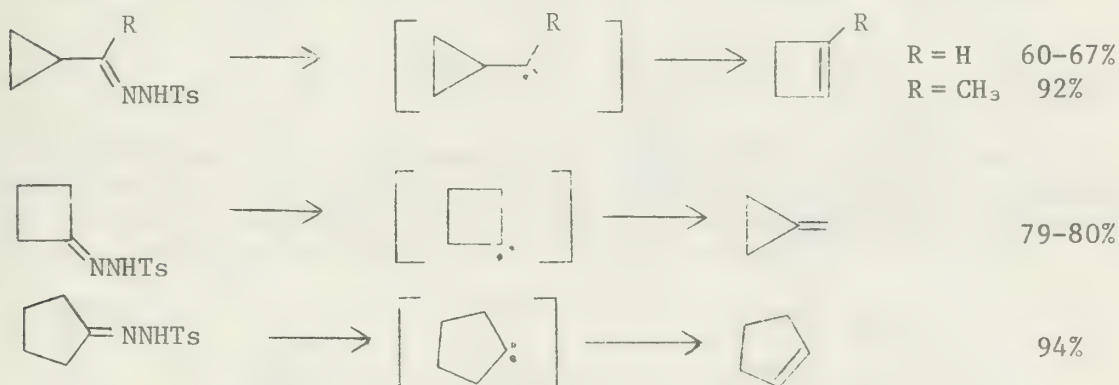
November 29, 1976

Carbenes are short-lived divalent carbon compounds known to be intermediates in a number of interesting reactions. Their tendency to insert into C-H bonds and to add to multiple bonds has been studied for some time. Recently, attention has focused on skeletal rearrangements of certain carbenes. This review will concentrate on those rearrangements which involve ring expansions or contractions. These reactions are basically of two types. Relief of strain in small ring carbenes provides one of the few driving forces rendering 1,2-migration competitive with intermolecular reactions. Other carbenes which rearrange in this manner contain β -phenyl or β -alkoxy substituents and will not be discussed here. The second type of ring expansion-contraction rearrangement, involving aromatic carbenes, has generated much interest in recent years. In many of these reactions alternatives to rearrangement are absent or much less likely to occur. Carbene rearrangements in general have been reviewed by Kirmse.¹ Gas phase aromatic carbene rearrangements are specifically covered by M. Jones, Jr.² A new series edited by Moss and Jones is an additional source of information on carbenes.³

For the most part the multiplicity of the unshared electron pair on the carbene carbon will be ignored in the following discussion. Most authors do not state whether a given carbene is singlet or triplet, but many use the singlet (bent) geometry in their mechanisms.

The most important of the 1,2-migrations involve cyclopropyl \rightleftharpoons cyclobutyl rearrangements and certain strained bicyclic compounds. Early work revealed good yields of cyclobutenes from cyclopropylcarbenes and of methylenecyclopropane from cyclobutylidene (Table 1).⁴ As ring size increases, the relative amount of ring expansion product drops until cyclopentylcarbene yields essentially no cyclohexene.^{4,5} Later work⁶ on the effect of protic

Table 1. Conditions: NaOMe, diethyl carbitol, 180°

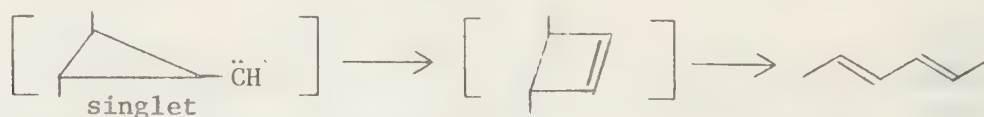


and aprotic solvents on product distribution showed the expansion of cyclobutylcarbene to cyclopentene to proceed by a cationic mechanism. Therefore, 1,2-migration appears to operate mainly in 3- and 4-membered rings.

Bicyclobutane was ruled out as an intermediate in ring expansion.⁷ Stereochemical studies provided further insight into the mechanism. Cyclopropylmethylcarbene rearranges to 1-methylcyclobutene (Table 1). Guarino and Wolf⁸ observed the variation in stereoselectivity as a function of

variation in conditions and proposed formation of singlet carbene which expands to cyclobutene with retention of configuration. The cyclobutene then undergoes a thermally allowed conrotatory ring opening to the observed product (Scheme I).

Scheme I



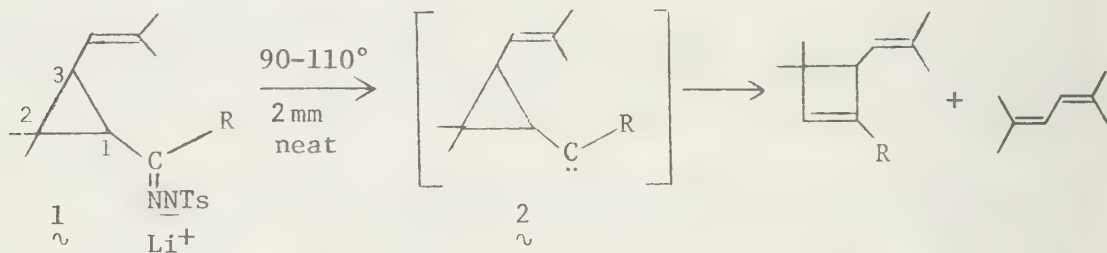
Conditions known to promote spin inversion to the triplet state cause loss of stereochemistry and reduced yield of diene. A study⁹ of unsymmetrical cyclopropylcarbenes led to the rather surprising result that migration of the less substituted bond was preferred (Table 2). Two explanations for this observation were offered. The possibility that the reaction does not really involve free carbene but rather loss of nitrogen synchronous with

Table 2.

	$\xrightarrow[135-140^\circ]{3 \text{ eq. NaOMe}}$ diglyme		85-90%
$R_1 = R_2 = \text{Me}$		2.5 : 97.5	
$R_1 = \text{Me}; R_2 = \text{H (cis)}$		4.4 : 95.6	
$R_1 = \text{H}; R_2 = \text{Me (trans)}$		27.9 : 72.1	

migration is countered by the fact that 3-cyclopropyl-3-methyldiazirine also produces 1-methylcyclobutene upon pyrolysis. The authors favored a free carbene mechanism in which the carbene carbon rotates into the plane of the ring causing steric interaction with ring substituents.

Recently, Sasaki, et. al.¹⁰ studied the products from the *cis* and *trans* isomers of chrysanthemylcarbenes 2a and 2b. Under conditions expected to



<u>trans-1a</u> ($R = \text{H}$)	32 : 68 (51%)
<u>cis-1a</u> ($R = \text{H}$)	27 : 73 (43%)
<u>trans-1b</u> ($R = \text{CH}_3$)	92 : 8 (95%)
<u>cis-1b</u> ($R = \text{CH}_3$)	70 : 30 (72%)

favor rearrangement, *cis*- and *trans*-2a yielded fragmentation product ~2:1 over migration product. In contrast, *cis*- and *trans*-2b showed high selectivity for migration over fragmentation with all of the migration occurring at the C_1-C_3 bond.

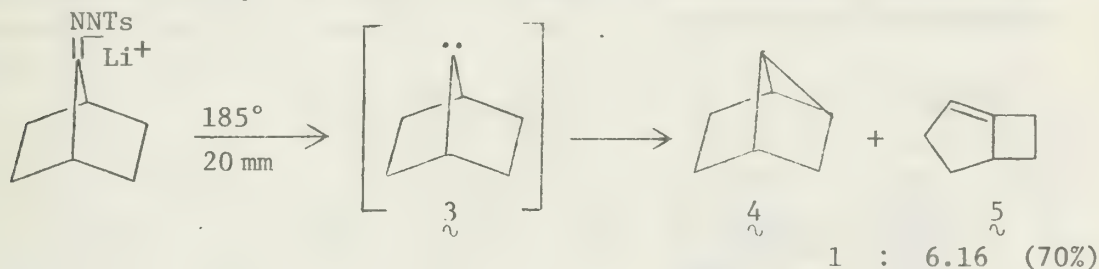
It was proposed that rearrangement to cyclobutene occurs from a conformation with an s-trans configuration about the carbene-cyclopropane bond. Due to steric hindrance, **2b** would be expected to assume this conformation to a greater extent than **2a**, partially explaining the observed differences in the proportion of rearranged product. For the same reason, trans-**2b** yields more cyclobutene than does cis-**2b**. An s-cis conformation leads to fragmentation products since migration would yield an impossibly strained trans-cyclobutene. Additionally, it was postulated that conjugation with the isobutenyl substituent lowers the transition state energy for fragmentation. Thus, the diene constitutes more of the product from **2a** than would otherwise be expected.

The observation that only the C₁-C₃ bond migrates during rearrangement was explained by electronic interaction between the carbene and the isobutenyl substituent similar to that postulated for the corresponding cation.

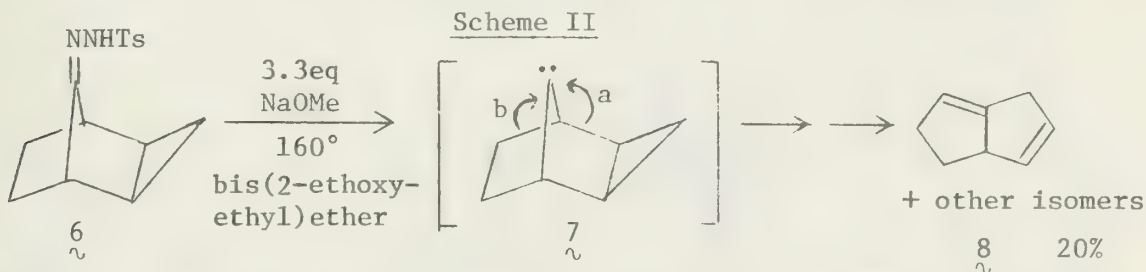
The authors proposed a cationic intermediate for decomposition of tosylhydrazone salt **1** in protic media and compared the reactions of cations and carbenes. They cite a number of references for comparison of similar cationic reactions.

Cyclobutylidene contraction and cyclopropylidene expansion have been used in several syntheses.¹¹⁻¹⁴

Bicyclic compounds constitute the other class of strained ring systems which might be induced to undergo ring expansion via generation of appropriately placed carbenes. Norbornan-7-ylidene (**3**) yielded two products in the ratio indicated.¹⁵ The bicyclic product **5** resulting from 1,2-migration is probably favored owing to the poor geometry for insertion leading to the tricyclic compound **4**.

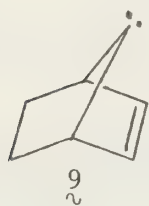


Decomposition of the analogous exo-8-tricyclo[3.2.1.0^{2,4}]octanone tosylhydrazone **6** provided a mixture of bicyclo[3.3.0]octadienes **8** consistent with an initial 1,2-migration from either side of the bridgehead (Scheme II). The alternatives were not distinguished in this work.¹⁶



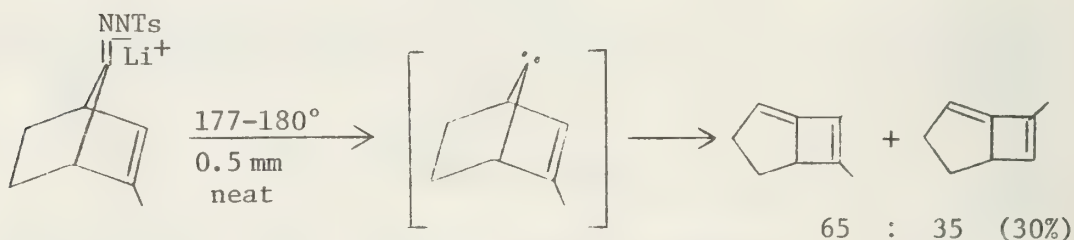
Moss¹⁷ has been interested in unsaturated bicyclic carbenes, such as **9**, which he terms "foiled methylenes". These carbenes give relatively lower

yields of products from self-insertion and intermolecular capture than do the saturated analogs. Intramolecularly the vinyl bridge migrates more readily than the saturated bridge. Moss and others propose that interaction between the π -electrons of the double bond and the empty p-orbital on the carbene stabilizes the molecule much as in the corresponding cation. Extended Huckel MO calculations which predict that the carbene bridge inclines $\sim 20^\circ$ toward the double bond¹⁸ support this proposal.



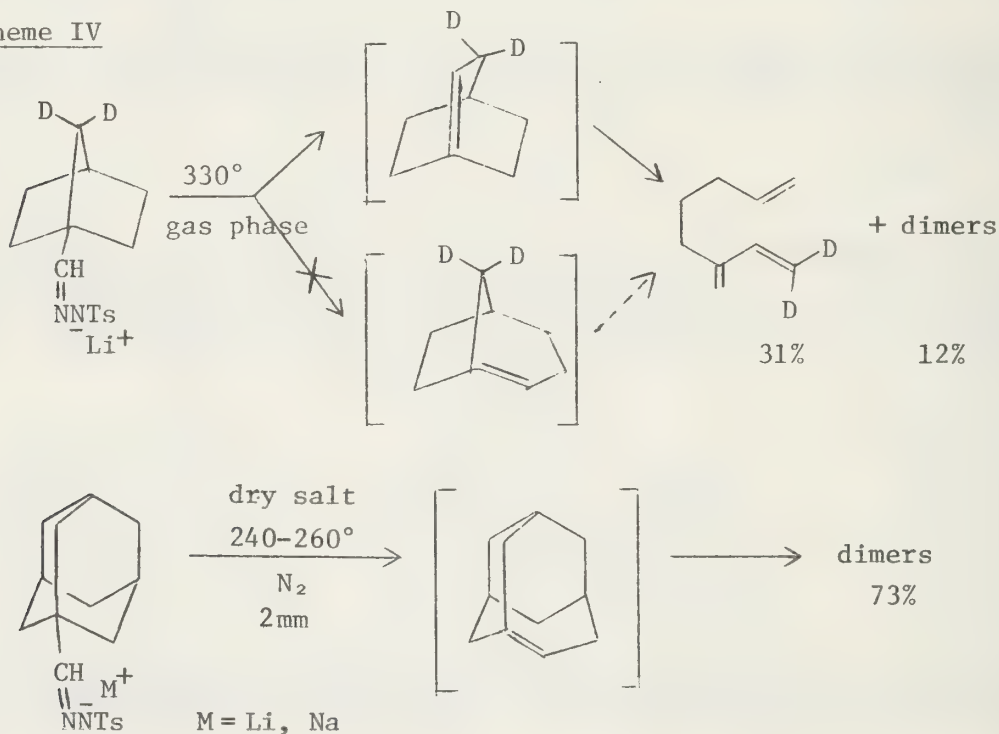
A labelling study using a methyl group showed a moderate substituent effect as indicated in Scheme III. The low selectivity indicates that the transition state does not acquire substantial carbonium ion character at the vinyl positions. The p- π interaction of carbene 9 is considered by these workers to be substantially weaker than that of the corresponding cation.

Scheme III

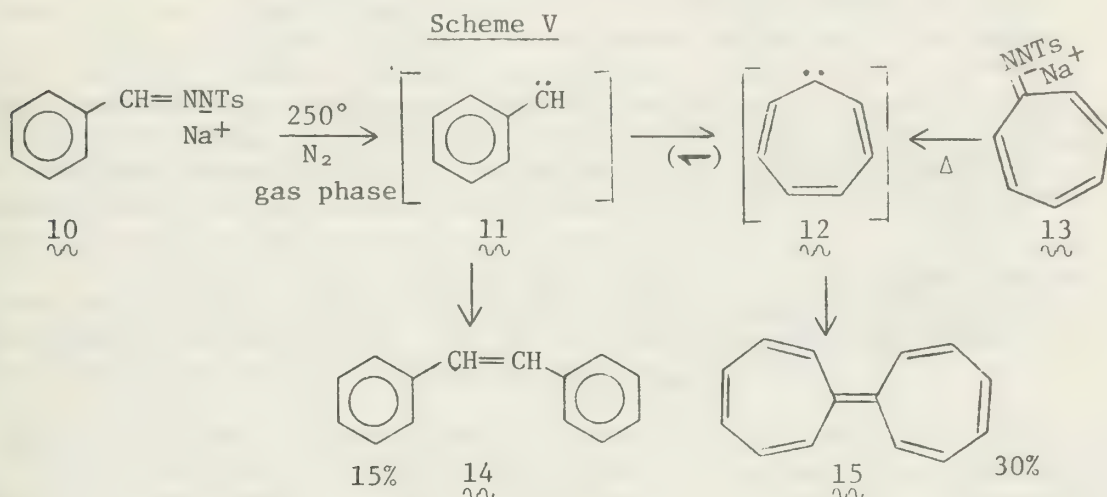


M. Jones, Jr.^{19,20} has generated exocyclic carbenes which appear to ring-expand to strained bridgehead olefins and subsequently rearrange. Two of the reactions are shown in Scheme IV. Also shown is the deuterium labelling experiment which demonstrated that the 1-norbornylcarbene expands only through migration of the short bridge. In neither case was the strained olefin isolated.

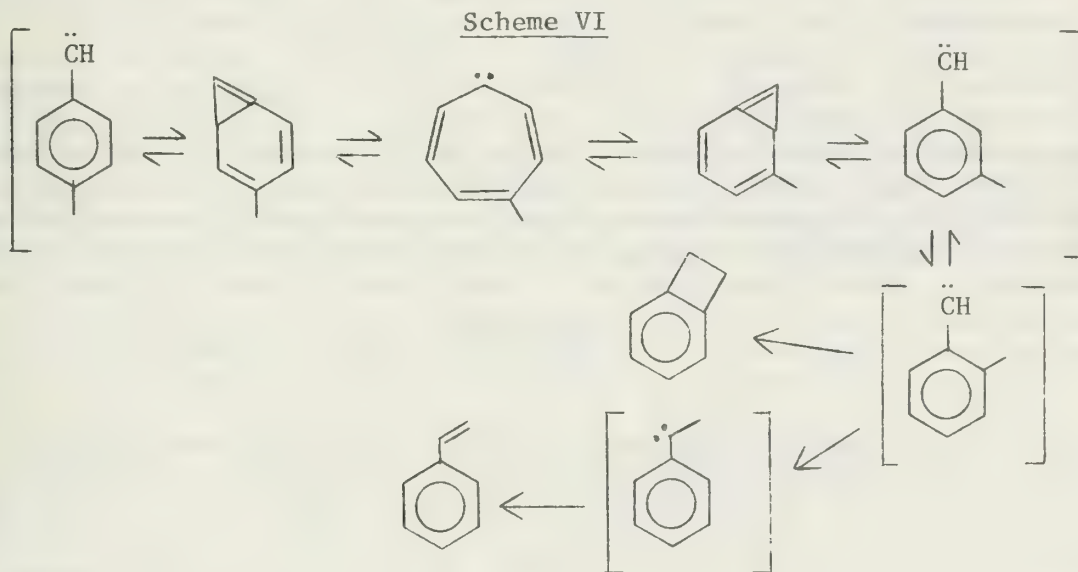
Scheme IV



In 1969, W. M. Jones and co-workers²¹ reported that the flash pyrolysis of the sodium salt of benzaldehyde tosylhydrazone **10** at 250° in a nitrogen stream gave not only stilbenes **14** as expected from dimerization of phenylcarbene **11**, but also heptafulvalene **15** in 30% yield. The latter product was identical to that obtained from the sodium salt of troponetotsylhydrazone **13** and suggested a common intermediate, probably cycloheptatrienylidene **12**. Since **13** afforded little or no stilbene, they concluded that either the rearrangement is irreversible or its equilibrium lies far to the right (Scheme V).



The next year, M. Jones, Jr., and co-workers²² reported evidence for the reversibility of the rearrangement. The three tolylcarbenes were generated by pyrolysis of the corresponding diazo compounds at low pressure. Each produced benzocyclobutene and styrene. The two products did not interconvert under the reaction conditions. Scheme VI was proposed to account for the results.

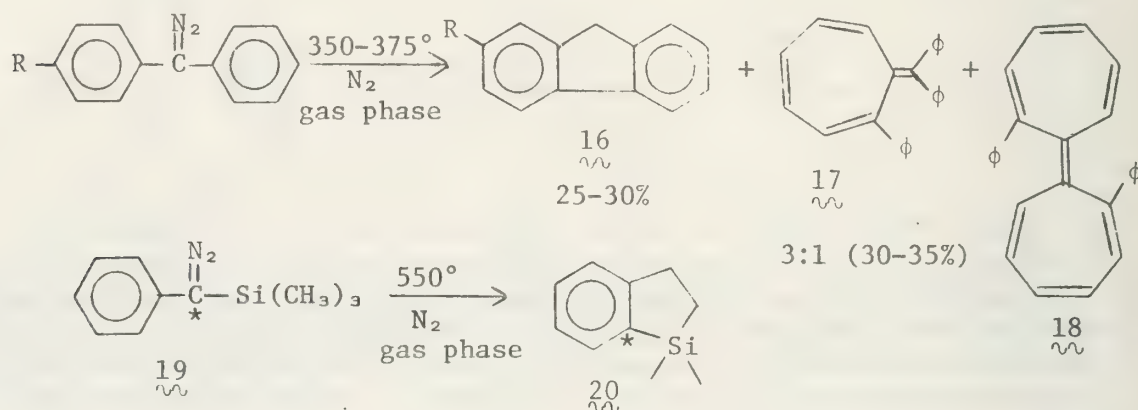


While mechanisms have been proposed which either convert one fused cyclopropene to another, bypassing the ring-expanded carbene, or involve a different intermediate between carbenes, most workers favor the mechanism in Scheme VI. Labelling studies, both with carbon and hydrogen isotopes and

with alkyl substituents on the ring, support the proposed mechanism and rule out certain other intermediates, such as a bicyclo[3.1.0]hexenyl diradical.^{23,24}

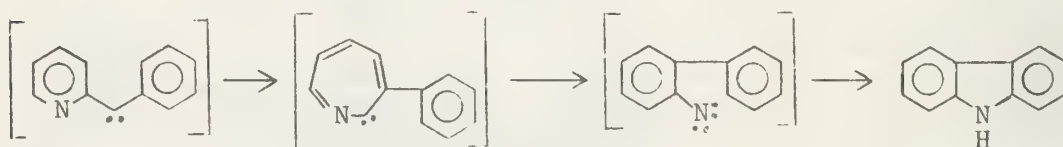
Recent work points to the discrete existence of the fused cyclopropene intermediate.²⁵⁻²⁷ Among the observations presented is the formation of several Diels-Alder products when an annelated carbene was generated in the presence of various dienes.²⁶

The carbene-carbene ring expansion-contraction nicely accounts for two reactions the mechanisms of which had not previously been satisfactorily explained. One is the formation of fluorene from diphenylcarbene. A *p*-methyl label on one ring produced labelled fluorene **16**, the expected product for this mechanism. The ring-expanded carbene also accounts for two other products, heptafulvalenes **17** and **18**.²⁸ Pyrolysis of phenyltrimethylsilyldiazomethane **19** to benzosilacyclopentene **20** can be explained by the same mechanism. ¹³C label at the site indicated confirmed the mechanism.²⁹

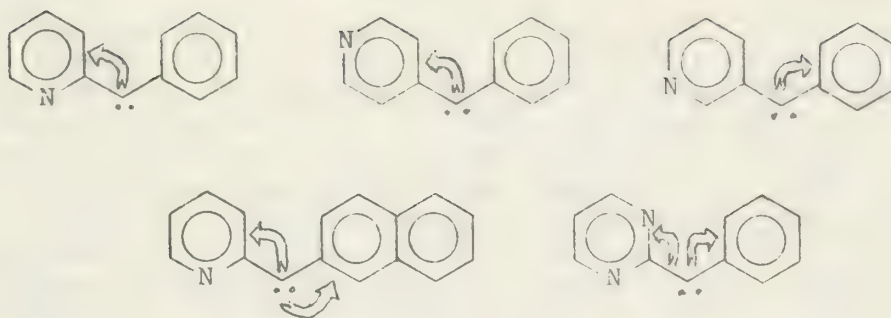


Recently, Mayor and Wentrup³⁰ examined the regioselectivity of the rearrangement of arylhetarylcarbenes by gas phase thermolysis of the corresponding diazo compounds at 380-900°, 10⁻³-10⁻² mm, giving aza analogs of fluorene. The evidence is consistent with the ring expansion-contraction mechanism discussed previously. For example, phenyl-2-pyridylcarbene rearranges to carbazole (Scheme VII). Labelling with ring substituents or carbon isotopes revealed the predominant regioselectivities summarized in Scheme VIII. The arrows point to the ring preferred for expansion in each case and the bond of that ring into which the carbene "inserts" preferentially.

Scheme VII

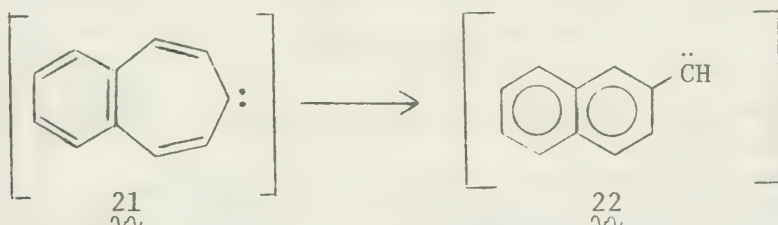


Scheme VIII



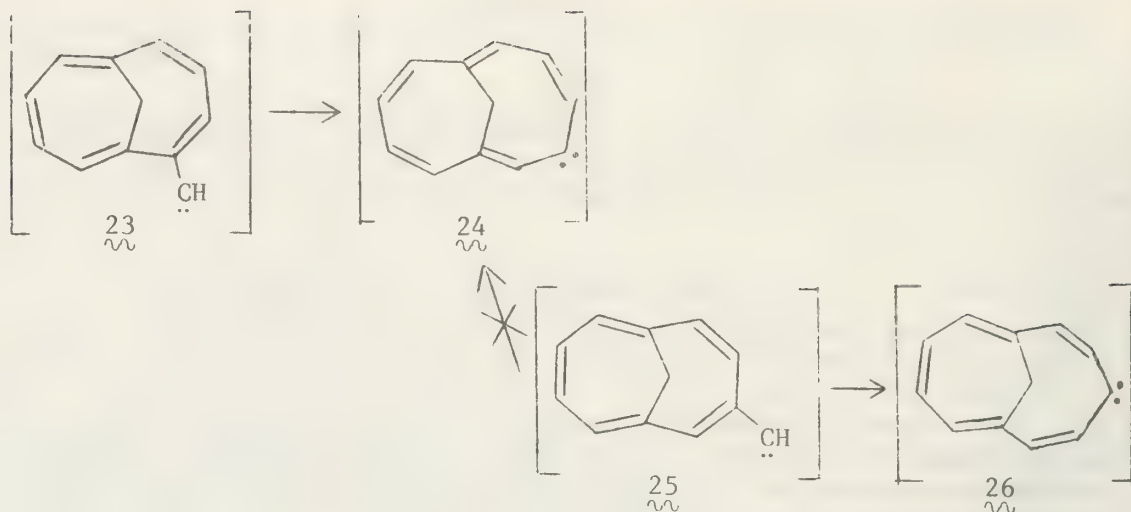
The authors exclude bond order and general susceptibility of the rings to electrophilic attack as explanations for their results. Instead, they propose a synergistic electrophilic-nucleophilic interaction in which the carbene donates its σ -electrons to the LUMO of the ring which is most electrophilic at the point of carbene attachment. In turn, the same ring donates its HOMO electrons to the empty p-orbital on the carbene from the most nucleophilic ortho position, the two interactions reinforcing each other. This mechanism implies that the interaction described above is involved in the product-determining transition state.

The first solution phase aromatic carbene rearrangement was reported in 1972.³¹ Although cycloheptatrienyliene does not rearrange in solution, the annelated carbene, benzocycloheptatrienyliene 21, rearranges to β -naphthylcarbene 22, as evidenced by $\sim 50\%$ yields of products from insertion or addition of the latter carbene to solvent. The reaction was carried out by



thermal decomposition at 100° or photolytic decomposition at room temperature or below of a solution of the sodium tosylhydrazone salt of 21. Rearrangement of the precursor was excluded and a fused cyclopropene intermediate was proposed. In contrast to the parent compound for which the ring-expansion products predominate,²¹ the annelated compound yields mostly ring-contraction products. These results have been rationalized through the use of INDO molecular orbital calculations.³² The effect of annelation on carbenes has been compared with its effect on cations.³¹

Two solution phase rearrangements of bridged annulenes have recently been studied. The first solution phase rearrangement of an exocyclic to an endocyclic carbene, 2-methano[10]annulenyliene 23 to 3,8-methano[11]annulenyliene 24, was carried out by thermal decomposition of the sodium tosylhydrazone salt in diglyme at 135° yielding up to 60% dimers of 24.³³ The intermediacy of 24 was confirmed by decomposition of its sodium tosylhydrazone salt to the same dimeric products. This reaction was significant in that previous solution phase reactions all involved ring contraction, whereas previous ring expansions had all occurred at high temperatures in the gas phase.



Brinker and Jones³⁴ reported the solution phase rearrangement of an isomer of 23. Methanoannulenylylidene 25 was generated at temperatures as low as -70° by photolysis of the sodium tosylhydrazone salt in diglyme. (Thermolysis gave only a pyrazole.) It rearranged to carbene 26 which subsequently formed a fulvalene dimer. Thermolysis of the sodium tosylhydrazone salt of 26 gave the same product and a mechanism similar to Scheme VI was proposed. No trace of products from the isomer 24 was detected which would indicate rearrangement to that carbene from 25.

A number of other aromatic carbene rearrangements are covered in references 35-37. Additional information on the similar arylnitrene rearrangements is available from references 30, 38, and 39.

BIBLIOGRAPHY

1. W. Kirmse, Ed., "Carbene Chemistry," 2nd ed, Academic Press, New York, 1971, Chapter 12.
2. M. Jones, Jr., *Acc. Chem. Res.*, 7, 415 (1974).
3. M. Jones, Jr. and R. A. Moss, Eds., "Carbenes," Vol. I-II, John Wiley & Sons, New York, 1973-75.
4. L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, 82, 1002 (1960).
5. H. G. Richey, Jr. and E. A. Hill, *J. Org. Chem.*, 29, 421 (1964).
6. D. H. Paskovich and P. W. N. Kwok, *Tetrahedron Lett.*, 2227 (1967).
7. J. A. Smith, H. Shechter, J. Bayless, and L. Friedman, *J. Am. Chem. Soc.*, 87, 659 (1965).
8. A. Guarino and A. P. Wolf, *Tetrahedron Lett.*, 655 (1969).
9. C. L. Bird, H. M. Frey, and I. D. R. Stevens, *J. Chem. Soc., Chem. Commun.*, 707 (1967).
10. T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *J. Org. Chem.*, 38, 4095 (1973), and references therein.
11. M. Rey, U. A. Huber, and A. S. Dreiding, *Tetrahedron Lett.*, 3583 (1968).
12. W. Kirmse and K. H. Pook, *Angew. Chem. Internat. Ed. Engl.*, 5, 594 (1966).
13. S. Nishida, I. Moritani, E. Tsuda, and T. Teraji, *J. Chem. Soc., Chem. Commun.*, 781 (1969).
14. R. R. Sauers, S. B. Schlosberg, and P. E. Pfeffer, *J. Org. Chem.*, 33, 2175 (1968).

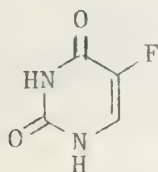
15. R. A. Moss and J. R. Whittle, J. Chem. Soc., Chem. Commun., 341 (1969).
16. P. K. Freeman, R. S. Raghavan, and D. G. Kuper, J. Am. Chem. Soc., 93, 5288 (1971).
17. R. A. Moss and C.-T. Ho, Tetrahedron Lett., 3397 (1976), and references cited therein.
18. R. Gleiter and R. Hoffmann, J. Am. Chem. Soc., 90, 5457 (1968).
19. M. Farcasiu, D. Farcasiu, R. T. Conlin, M. Jones, Jr., and P. von R. Schleyer, J. Am. Chem. Soc., 95, 8207 (1973).
20. A. D. Wolf and M. Jones, Jr., J. Am. Chem. Soc., 95, 8209 (1973).
21. R. C. Joines, A. B. Turner, and W. M. Jones, J. Am. Chem. Soc., 91, 7754 (1969).
22. W. J. Baron, M. Jones, Jr., and P. P. Gaspar, J. Am. Chem. Soc., 92, 4739 (1970).
23. E. Hedaya and M. E. Kent, J. Am. Chem. Soc., 93, 3283 (1971).
24. G. G. Vander Stouw, A. R. Kraska, and H. Shechter, J. Am. Chem. Soc., 94, 1655 (1972).
25. W. E. Billups, L. P. Lin, and W. Y. Chow, J. Am. Chem. Soc., 96, 4026 (1974).
26. T. T. Coburn and W. M. Jones, J. Am. Chem. Soc., 96, 5218 (1974).
27. J. P. Mykytka and W. M. Jones, J. Am. Chem. Soc., 97, 5933 (1975).
28. J. A. Myers, R. C. Joines, and W. M. Jones, J. Am. Chem. Soc., 92, 4740 (1970).
29. T. J. Barton, et al., J. Am. Chem. Soc., 97, 657 (1975).
30. C. Mayor and C. Wentrup, J. Am. Chem. Soc., 97, 7467 (1975), and references cited therein.
31. (a) K. E. Krajca, T. Mitsunashi, and W. M. Jones, J. Am. Chem. Soc., 94, 3661 (1972); (b) W. M. Jones, et al., ibid., 95, 826 (1973).
32. R. L. Tyner, W. M. Jones, Y. Ohrn, and J. R. Sabin, J. Am. Chem. Soc., 96, 3765 (1974).
33. R. A. LaBar and W. M. Jones, J. Am. Chem. Soc., 96, 3645 (1974).
34. U. H. Brinker and W. M. Jones, Tetrahedron Lett., 577 (1976).
35. P. Schissel, M. E. Kent, D. J. McAdoo, and E. Hedaya, J. Am. Chem. Soc., 92, 2147 (1970).
36. T. J. Katz, J. J. Cheung, and N. Acton, J. Am. Chem. Soc., 92, 6643 (1970).
37. T. T. Coburn and W. M. Jones, Tetrahedron Lett., 3905 (1973).
38. C. Thetaz and C. Wentrup, J. Am. Chem. Soc., 98, 1258 (1976).
39. R. Harder and C. Wentrup, J. Am. Chem. Soc., 98, 1259 (1976).

NEW METHODS FOR SELECTIVE INTRODUCTION OF FLUORINE INTO ORGANIC COMPOUNDS

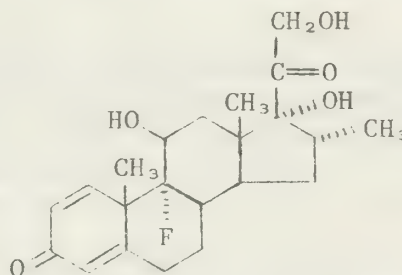
Reported by Alphonse McMahon

December 6, 1976

The selective introduction of fluorine into organic compounds has been a problem of recent interest to organic chemists. One fluorine atom introduced into an organic molecule is potentially valuable as a probe (nmr) for biological, mechanistic and structural studies or to alter biological activity or chemical reactivity. The basis for the change in biological activity can be summarized by the following four points: 1) Fluorine, the second smallest "atom" as measured by atomic radius and internuclear distance to carbon, would most closely resemble bioactive hydrogen analogs with respect to steric requirements at enzyme receptor sites. 2) Due to its high electronegativity, electronic effects can be altered to a great extent. 3) Fluorine imparts increased oxidative and thermal stability because the binding energy of the C-F bond exceeds that of the C-H bond by 10-20 kcal/mole.¹ However, improved stability may lead to pitfalls, such as a "lethal" synthesis of fluoroacetate. 4) Finally, introduction of fluorine leads to increased lipid solubility in membranes that would enhance the rates of absorption and transport *in vivo*.² Two examples of compounds whose biological activities have been altered through selective introduction of fluorine are 5-fluorouracil (1), which has significant tumor-inhibiting activity, and dexamethasone (2), one of the most potent antiarthritic steroids known.²



1



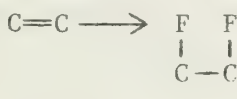
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This seminar will be divided into two main parts, the first dealing with methods of introducing fluorine into the aliphatic portion of a molecule and the second part covering aromatic fluorination. Aliphatic fluorination can be subdivided into three areas: oxidative fluorinations, displacement by fluoride and hydrofluorination. Methods of aromatic fluorination consist of direct and indirect substitution of fluorine on the aromatic nucleus.

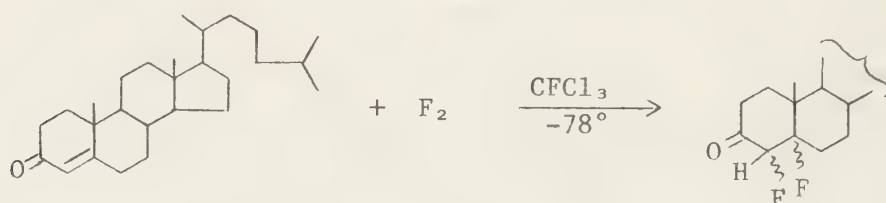
FLUORINATION OF ALIPHATIC COMPOUNDS

A good review on some of the newer methods of aliphatic monofluorination has been written by Sharts and Sheppard.^{4a}

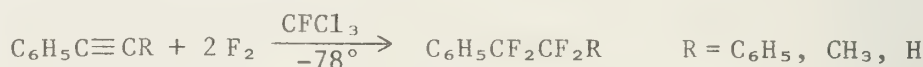
1. Oxidative Fluorination. Six reagents fall into this category: elemental fluorine, high-valence metal fluorides, xenon difluoride, perchloryl fluoride, nitrosyl fluoride and trifluoromethyl hypofluorite. Electrochemical fluorination, in which an organic compound is electrolyzed in liquid hydrogen fluoride at 0°C, is a method for preparing perfluorinated compounds.^{1,3a-c} It will not be discussed further.



The direct reaction of fluorine with organic compounds usually gives extensive degradation and fragmentation of the starting materials. More recently, this problem has been minimized by diluting the fluorine with an inert gas such as helium or nitrogen and working at a low temperature (-78°) in an inert solvent (CFCl_3), or by using a high-valence metal which can oxidatively fluorinate an organic compound. Thus, elemental fluorine can add to the double bond of 4-cholesten-3-one to give the cis-4,5-difluoride



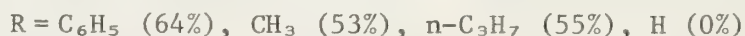
in 60-70% yield.^{5a} It has also been used to fluorinate acetylenes:^{4b}



There are, however, certain problems involved in working with elemental fluorine. It attacks double bonds, glassware, and chemists with equal vigor; consequently, special apparatus must be constructed (polytetrafluoroethylene, polychlorotrifluoroethylene, and Monel metal are used) and elaborate safety precautions maintained.

High-valence metal fluorides, such as silver (II) fluoride, cobalt (III) fluoride, and lead (IV) fluoride, are even less useful than elemental fluorine for selective fluorination. The cobalt and silver fluorides react with aromatic compounds to give completely saturated cyclic fluorocarbons.^{6a,b} Lead (IV) fluoride is more selective, adding the elements of fluorine across a double bond, although rearrangements occur.⁷

Xenon difluoride is a rather unique fluorinating reagent. This exotic compound can be prepared via a photochemical or thermal reaction of xenon and fluorine, and is a stable solid.^{8a,b} 1,1-diphenylethylenes are fluorinated in an acid-catalyzed reaction at room temperature to give the 1,2-difluoroethanes in 65-95% yields.⁹ 1-phenylacetylenes react as shown below:¹⁰

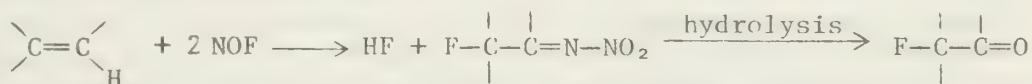


Xenon difluoride has also been used to prepare 5-fluorouracil (1) in one step from uracil (10%)¹¹ and reacts with adamantane to give the 1-fluoro derivative in 35% yield.¹²



Perchloryl fluoride (FClO_3), a gaseous reagent, is used to introduce fluorine selectively in place of hydrogen in active methylene compounds. Its use has been described in the review by Sharts and Sheppard.^{4b} This method of fluorination has been applied to a wide variety of active methylene compounds such as α -keto esters, enol ethers, enamines, enamides, gem-dinitriles, nitroalkanes and phenols (as dienones). Organometallic compounds can also be monofluorinated. Perchloryl fluoride is simple to use but precautions must be taken since it is a powerful oxidizing agent.

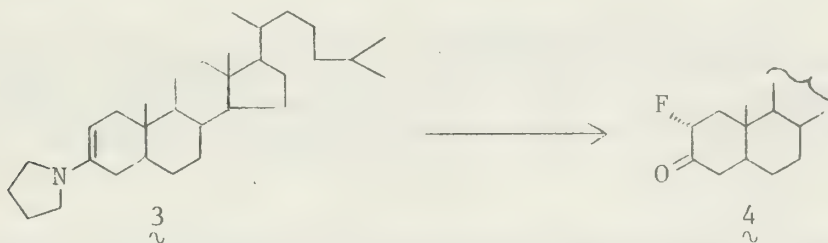
Nitrosyl fluoride (NOF) is a new reagent that provides a controlled method of monofluorination. Until recently, reactions with organic substrates were mostly limited to highly fluorinated olefins and other fluorinated unsaturated compounds.^{13a-c} Boswell^{14a,b} found that by proper choice of conditions, NOF could be used to introduce a single fluorine atom into steroids. Initial addition of F-NO to a double bond is followed by reaction of the adduct with a second molecule of nitrosyl fluoride to give a nitrimine; hydrolysis leads to the α -fluoroketone. Nitrosyl fluoride usually adds only to electron-rich double bonds.



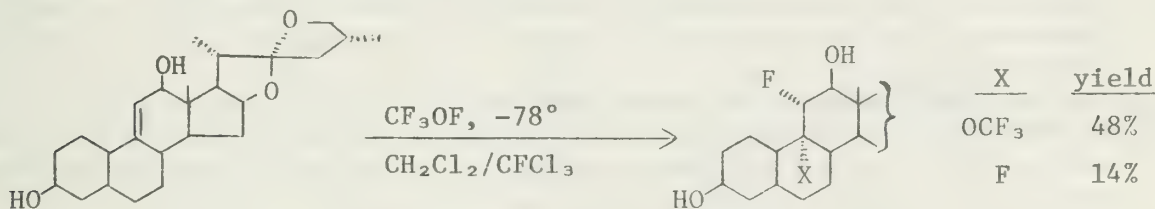
The reaction is run by bubbling nitrosyl fluoride in at ice bath temperature. Yields of the fluoronitrimine range from 45-66%.^{4c}

Recently hypofluorites, primarily trifluoromethyl hypofluorite (CF_3OF), have been developed as useful reagents for electrophilic fluorination. Some of the uses of these reagents have been reviewed by Sharts and Sheppard.^{4d} A strong electronegative group such as perfluoroalkyl is required to stabilize the hypofluorite group and activate the O-F bond for electrophilic reaction. Thus, trifluoromethyl hypofluorite, a commercially available reagent,¹⁵ adds a new dimension to fluorination; $\text{CF}_3\text{O}-\text{F}$ adds to olefinic or other unsaturated centers, and the CF_3O group can often be hydrolyzed to leave a monofluoro product. Photofluorination of organic molecules using CF_3OF has also been described.^{16a,b}

Trifluoromethyl hypofluorite reacts with electron-rich olefins like 3-pyrrolidylcholest-2-ene (**3**)¹⁷ in the same way as perchloryl fluoride¹⁸ to furnish 2 α -fluorcholestanone (**4**) in good yield.



CF_3OF also reacts with unactivated double bonds as shown:

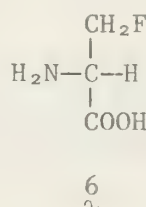
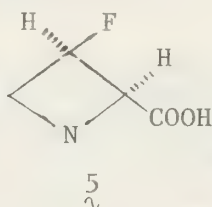


Mild base hydrolysis of the $\text{F}-\text{OCF}_3$ adduct gave the vinyl fluoride.¹⁹ Another electrophilic fluorination, analogous to FCIO_3 , afforded 5-fluorouracil (**1**) in 85% yield.²⁰

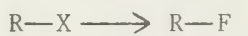


There have been two reports of the selective replacement of a hydrogen attached to an unactivated, saturated carbon with trifluoromethyl hypofluorite or elemental fluorine. The reaction of adamantane with CF_3OF (-25°) gives 1-fluoroadamantane (75%).²¹ The reaction was viewed as involving direct electrophilic attack on the electrons of the C-H σ bond leading to a species with a "nonclassical" three-center, two electron bond. The classical adamantyl "cation," if formed, would lead, by the capture of CF_3O^- , to substantial amounts of adamantyl trifluoromethyl ether, which is not isolated. This reaction, by virtue of its highly polar transition state, should be extremely sensitive to the inductive effect of polar substituents, even those present at remote sites. Thus, selective functionalization at the 9α , 14α , and 17α positions of the steroid skeleton with either elemental fluorine or trifluoromethyl hypofluorite (with radical inhibitor) can be accomplished in 34-40% yield.²² This comprises an effective, predictable, regioselective process for substitution at saturated carbon.

Photofluorination using CF_3OF has not been widely investigated. A communication^{16a} described the photofluorination of L-azetidine-2-carboxylic acid in liquid hydrogen fluoride at -78° to yield cis-3-fluoro-L-azetidine-2-carboxylic acid (**5**) (53%). In a more recent article,^{16b} D-alanine was subjected to the same reaction conditions to afford 3-fluoro-D-alanine (**6**) in 57% yield. There is no racemization observed, thus optically active fluorinated amino acids become easily available.



2. Displacement by Fluoride. There are a number of reagents that effect displacement by fluoride: group I fluorides, hydrogen fluoride (with catalyst, in pyridine, or with an oxidizing agent), the fluoroalkylamine reagent, sulfur tetrafluoride and dialkylaminosulfur trifluorides.



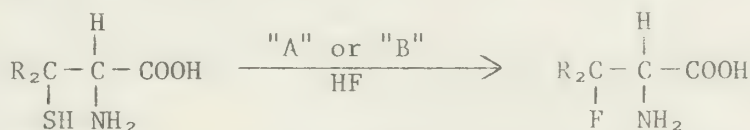
Potassium fluoride is the most useful alkali metal fluoride for substitution of fluorine for halogen or an oxygen-bonded function. However, the oxygen-bonded function must be activated (e.g., as a tosylate) before displacement. Reaction in a polar solvent permits fluorinations at lower temperatures. Higher yields are obtained if the halogen displaced is alpha to an activating group, such as an ester, nitrile or amide. If unactivated, only primary halogens can be successfully displaced.²³ Use of crown ether reagents to complex the metal salt increases its solubility in both polar and non-polar aprotic solvents. Primary halides give predominantly the substitution product, whereas secondary halides give predominantly or exclusively alkene products.²⁴ This is explained by the fact that fluoride ion, unencumbered by strong solvation forces, is both a potent nucleophile and base.²⁵ Classically, silver (I) fluoride was used for controlled fluorination of partially halogenated alkyl halides. They have been supplanted to a great extent by potassium fluoride in polar nonaqueous solvents.²⁶

Hydrogen fluoride can be used to substitute a fluorine for a halogen or oxygen-bonded group such as a p-toluenesulfonate group, but an antimony (III) or antimony (V) fluoride catalyst is usually needed. The $-\text{CH}_2\text{Cl}$ and

>CHCl groups are extremely resistant to fluoride substitution and only rarely give the mono-fluoro product. This hydrogen fluoride-catalyst method appears to be most effective for -CCl_3 and >CCl_2 .²⁷

A newer development with hydrogen fluoride has been reported. Olah^{28a-c} has found that a 70% (w/w) solution of hydrogen fluoride in pyridine is stable and does not lose hydrogen fluoride to any degree when warmed up to 50°. ^{28a} The reagent has been used to fluorinate secondary and tertiary alcohols. ^{28b} When cyclohexane is added to a hydrogen fluoride-pyridine solution, an immiscible upper layer forms in which the alkyl fluoride products are very soluble, thus minimizing possible side reactions. Several simple aliphatic alcohols, 2-norbornyl alcohol, 1-adamantyl alcohol, α -phenylethyl alcohol, and triphenylmethyl alcohol were all successfully fluorinated in yields generally greater than 70%. This reagent has also been used to prepare α -fluorocarboxylic acids from α -amino acids via diazotization in the hydrogen fluoride-pyridine solution. ^{28c} These fluoroacids, previously available only in low yield, ^{28c} can now be obtained in yields ranging from 12 to 98%.

There is one example of the use of an oxidizing agent (trifluoromethyl hypofluorite, N-chlorosuccinimide, elemental chlorine, or elemental fluorine) in hydrogen fluoride to replace the -SH group by fluoride. ²⁹



"A" = either CF_3OF , NCS, or Cl_2 R = CH_3 (94% yield)

"B" = 1:4 v/v F_2/He R = H (33% yield)

Mechanistically, the reagent is seen to act as an oxidizing agent to transform the thiol into a good leaving group.



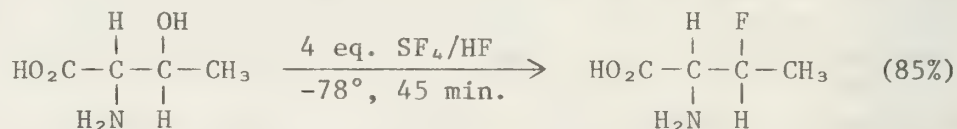
Several observations support this hypothesis. When trifluoromethyl hypofluorite is used with trifluoroacetic acid as the catalyst, no fluoro product is formed which leads to the conclusion that the fluoride comes from the solvent. Sulfur difluoride is known to disproportionate to sulfur and sulfur tetrafluoride, ³⁰ and, when CF_3OF is used, elemental sulfur is obtained.

Since the conversion of primary thiols (such as cysteine (R=H)) to fluorides requires the more powerful oxidizing agent, F_2/He , more potent leaving groups may be necessary to effect the displacement.

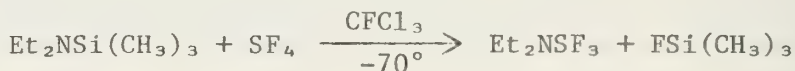
The one-step conversion of a hydroxy derivative to the corresponding fluoro compound by 2-chloro-1,1,2-trifluorotriethylamine ($(\text{C}_2\text{H}_5)_2\text{NCF}_2\text{CHClF}$), known as the fluoroalkylamine reagent (FAR), is a valuable synthetic method. Its preparation and uses have been described. ^{4e} FAR replaces primary aliphatic alcohols by fluorine in high yields with limited side reactions. Secondary alcohols usually react cleanly with FAR to give the corresponding fluorides. ³¹ With cyclic secondary alcohols the elimination side reaction often predominates. ³² Tertiary alcohols rarely give tertiary fluorides; in most cases, side reactions predominate. ³⁰ The fluorination of alcohols by FAR is one of the simplest, most convenient, and safest fluorination

techniques. The alcohol is dissolved in an inert solvent (such as diethyl ether, methylene chloride or tetrahydrofuran), a 50-100% excess of FAR is added at 0-25°, and the reaction mixture is allowed to stand 3-24 hr. and is worked up.

Sulfur tetrafluoride has been used to some extent in replacing hydroxyl by fluoride. However, it works well only for acidic alcohols. An extensive review on the subject is available.³³ For example, in liquid hydrogen fluoride, sulfur tetrafluoride selectively replaces the hydroxyl group in hydroxy amines and hydroxy amino acids.³⁴ L-threonine was converted to L-2-amino-3-fluorobutyric acid.

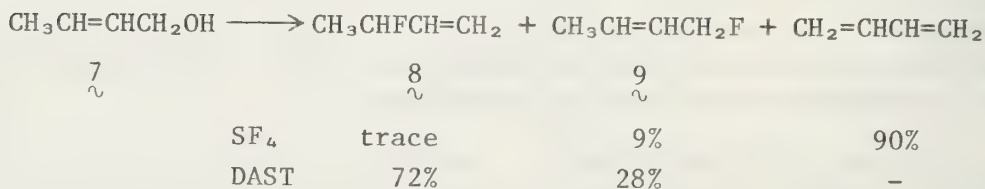
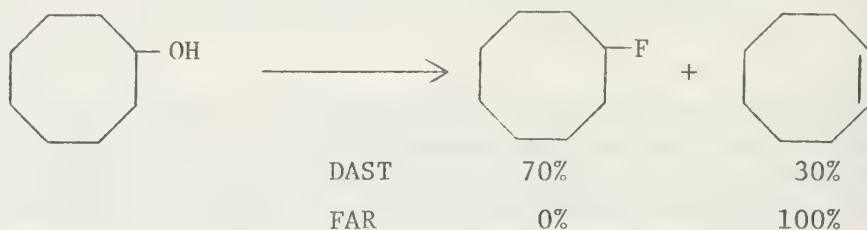


Dialkylaminosulfur trifluorides (R₂NSF₃) are analogs of sulfur tetrafluoride that are used for displacing hydroxyl with fluoride. Diethylaminosulfur trifluoride (DAST) is the major reagent used. Its preparation is as follows:

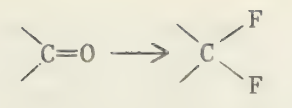


This trifluoride is a stable product that can be distilled and stored in a plastic container at room temperature.³⁵

The reactions are conducted under very mild conditions so that other groups, including ester groups and other halogens, can also be present. Typically, the alcohol is added slowly to a solution of DAST in an inert solvent (dichloromethane, trichlorofluoromethane, diglyme) cooled to -50° to -78°. Primary, secondary, and tertiary alcohols all react with high yields of the unrearranged fluoride usually resulting.³⁵

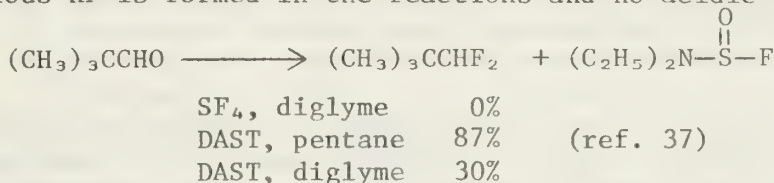


Bis(dialkylamino)sulfur difluorides are also useful reagents for replacing hydroxyl groups with fluoride in sensitive alcohols. Although they are less reactive, the difluorides have certain advantages in that they cause less rearrangement and elimination. Crotyl alcohol (7), which is sensitive to both double bond rearrangement and dehydration, reacts with diethylaminodimethylaminosulfur difluoride to give the unrearranged 9 and the rearrangement product 8 in a 72:21 ratio.³⁵



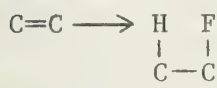
As stated above, sulfur tetrafluoride can be used to effect $\text{R-OH} \rightarrow \text{R-F}$. However, its greatest utility is in converting carbonyl oxygen to a gem-difluoro compound. The reaction has broad scope and is effective with virtually all carbonyl compounds, including acid halides, aldehydes, ketones, and quinones. Hydrogen fluoride and Lewis acids catalyze the reaction.³⁶

DAST is a useful reagent for fluorination of aldehydes and ketones, particularly those sensitive to acidic conditions, since no acid other than adventitious HF is formed in the reactions and no acidic catalyst is needed.



DAST appears to be one of the best reagents for replacement of alcohols by fluorides and gem-difluorination of aldehydes and ketones.

3. Hydrofluorination.

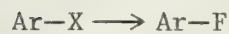


Alkenes usually add hydrogen fluoride between -78° and 0° . Alkynes undergo hydrogen fluoride addition readily to give geminally substituted difluoroalkanes at low temperatures.³⁸

Olah's hydrogen fluoride-pyridine reagent effects the addition of hydrogen fluoride to olefins with tetrahydrofuran as a co-solvent at room temperature to give the corresponding fluoroalkanes in yields generally greater than 65%.^{28a}

FLUORINATION OF AROMATIC COMPOUNDS

1. Indirect Substitution.



The best-known method for the selective introduction of fluorine into aromatic compounds is the Balz-Schieman reaction. A primary aromatic amine is diazotized and the diazonium tetrafluoroborate salt precipitated, dried, and pyrolyzed to the aromatic fluoride. Availability and stability of the requisite amine, substituents on the ring which may interfere in diazotization or pyrolysis, and solubility of the tetrafluoroborate salt are some of the problems that can arise in a synthesis.³⁹ A modification involves the use of hexafluorophosphoric acid to form the hexafluorophosphate salt. They are less soluble in water and are stable in anhydrous form to both shock and heat, regardless of the ring substituents.⁴⁰

Pyrolysis of aryl fluoroformates,^{41a-c} catalytic decarbonylation⁴² of aroyl fluorides, and fluorine-chlorine exchange reactions^{43,44} are older methods for the introduction of fluorine into an aromatic nucleus.

2. Direct Substitution.



There have been few successful examples of fluorination of aromatic compounds with trifluoromethylhypofluorite. Irradiation of benzene in the presence of CF_3OF gave a 65% yield of fluorobenzene.^{16a} Treatment of salicylic acid with CF_3OF gave a 4:1 mixture of 5- and 3-fluorosalicylic acids (70%).⁴⁵ β -Substituted naphthols gave mostly fluorine addition products with some (9-25%) fluorine substitution at the alpha position.⁴⁶ Electrophilic fluorination of aromatic compounds by CF_3OF appears to have limited utility but can be expected as a complicating side reaction in reactants containing an aromatic ring.

Xenon difluoride reacts with substituted benzenes (32-81% yield),⁴⁷ polycyclic aromatics (pyrene,^{48e} phenanthrene,^{48a,c,d} naphthalene,^{48d} anthracene,^{48d} and benzo[a]pyrene^{48b}), aryl oxygen compounds (38-71%),^{48f} nitrogen-containing aromatics (40-56%),^{48g} and estrone-3-methyl ether^{48h} to give aromatic fluorides. Substituent effects are similar to those observed in electrophilic aromatic substitution reactions.⁴⁷ The presence of hydrogen fluoride as a catalyst appears to be necessary. These reactions are carried out in methylene chloride or chloroform at temperatures from -78 to 25°. Xenon difluoride offers an attractive alternative to the conventional methods of preparing aromatic fluorides.

BIBLIOGRAPHY

1. W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, Inc., New York, 1969, p. 27.
2. R. Filler, *Chemtech*, 752 (1974).
3. (a) F. G. Drakesmith and D. A. Hughes, *J. Appl. Electrochem.*, **6**, 23 (1976); (b) K. Okazaki, S. Nagase, H. Baba and K. Kodaira, *J. Fluo. Chem.*, **4**, 387 (1974); (c) Y. Inoue, S. Nagase, K. Kodaira, H. Baba and T. Abe, *Bull. Chem. Soc., Japan*, **46**, 2204 (1973).
4. (a) C. M. Sharts and W. A. Sheppard, *Org. React.*, **21**, 159 (1974); (b) *ibid.*, pp. 225-236; (c) *ibid.*, pp. 242-243; (d) *ibid.*, pp. 243-256; (e) *ibid.*, pp. 147-173; (f) *ibid.*, p. 160.
5. (a) R. F. Merritt and T. E. Stevens, *J. Am. Chem. Soc.*, **88**, 1822 (1966); (b) R. F. Merritt, *J. Org. Chem.*, **32**, 4124 (1967).
6. (a) R. G. Plevy, M. P. Steward, and J. C. Tatlow, *J. Fluo. Chem.*, **3**, 259 (1973/74); (b) P. L. Coe, R. M. Habib, and J. C. Tatlow, *J. Fluo. Chem.*, **5**, 19 (1975).
7. D. D. Tanner and P. V. Bostelen, *J. Am. Chem. Soc.*, **94**, 3187 (1972).
8. (a) J. L. Weeks, C. L. Chernick, and M. S. Matheson, *J. Am. Chem. Soc.*, **84**, 4612 (1962); (b) F. Schreiner, G. N. McDonald, and C. L. Chernick, *J. Phys. Chem.*, **72**, 1162 (1968).
9. M. Zupan and A. Pollak, *J. Chem. Soc., Chem. Commun.*, 845 (1973).
10. M. Zupan and A. Pollak, *J. Org. Chem.*, **39**, 2646 (1974).
11. T. I. Yurasova, *Zh. Obshch. Khim.*, **44**, 956 (1974).
12. A. T. Podkhalyuzin and M. P. Nazarova, *Zh. Org. Khim.*, **11**, 1568 (1975).
13. (a) S. Andreades, *J. Org. Chem.*, **27**, 4157 (1962); (b) B. L. Dyatkin, E. P. Mochalina, R. A. Bekker, S. R. Sterlin, and I. L. Knunyants, *Tetrahedron*, **23**, 4291 (1967); (c) R. Schmutzler, *Angew. Chem., Int. Ed. Engl.*, **7**, 440 (1968).

14. (a) G. A. Boswell, Jr., Chem. Ind. (London), 1929 (1965); (b) *ibid.*, J. Org. Chem., 33, 3699 (1968).
15. PCR Inc., P.O. Box 1466, Gainesville, Florida 32601.
16. (a) J. Kollonitsch, L. Barash and G. A. Doldouras, J. Am. Chem. Soc., 92, 7494 (1970); (b) J. Kollonitsch and L. Barash, *ibid.*, 98, 5591 (1976).
17. D. H. R. Barton, R. H. Hesse, L. Ogunkoya, N. D. Westcott, and M. M. Pechet, J. Chem. Soc., Perkin I, 2889 (1972).
18. J. S. Mills, J. Barrera, E. Olivares, and H. Garcia, J. Am. Chem. Soc., 82, 5882 (1960).
19. D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, J. Chem. Soc., Perkin I, 101 (1976).
20. D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, J. Org. Chem., 37, 329 (1972).
21. D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, and H. T. Toh, J. Am. Chem. Soc., 98, 3034 (1976).
22. D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, H. T. Toh, and S. Rozen, *ibid.*, 98, 3036 (1976).
23. F. L. M. Pattison, R. L. Buchanan, and F. H. Dean, Can. J. Chem., 43, 1700 (1965).
24. C. L. Liotta and H. P. Harris, J. Am. Chem. Soc., 96, 2250 (1974).
25. See ref. 1, pp. 14-17.
26. See ref. 1, p. 81.
27. A. K. Barbour, L. J. Belf, and M. W. Buxton, Adv. Fluor. Chem., 3, 181 (1963).
28. (a) G. A. Olah, M. Nojima, and I. Kerekes, Synthesis, 779 (1973); (b) *ibid.*, 786 (1973) (c) G. A. Olah and J. Welch, *ibid.*, 652 (1974).
29. J. Kollonitsch, S. Marburg, and L. M. Perkins, J. Org. Chem., 41, 3107 (1976).
30. F. Seel, E. Heinrich, W. Gombler, and R. Budenz, Chimia, 23, 73 (1969).
31. M. Hudlicky and I. Lejhancova, Coll. Czech. Chem. Comm., 31, 1416 (1966).
32. E. L. Eliel and R. J. L. Martin, J. Am. Chem. Soc., 90, 682 (1968).
33. G. A. Boswell, W. C. Ripka, R. M. Scribner, and C. W. Tullock, Org. React., 21, pp. 12-20 (1974).
34. J. Kollonitsch, S. Marburg, and L. M. Perkins, J. Org. Chem., 40, 3808 (1975).
35. W. J. Middleton, *ibid.*, 574.
36. See ref. 33, pp. 1-124.
37. W. J. Middleton, Abstracts of Papers, Gordon Research Conf., pp. 8-10 (1975).
38. K. Matsuda, J. A. Sedlak, J. S. Noland, and G. C. Glecker, J. Org. Chem., 27, 4015 (1962).
39. N. Ishikawa and T. Kitazume, J. Syn. Org. Japan, 34, 173 (1976).
40. (a) K. G. Rutherford, W. Redmond, and J. Rigamonti, J. Org. Chem., 26, 5149 (1961); (b) *ibid.*, Org. Syn., 43, 12 (1960).
41. (a) K. O. Christie and A. E. Pavlath, J. Org. Chem., 30, 3170 (1965); (b) *ibid.*, 4104 (1965); (c) *ibid.*, 31, 559 (1966).
42. G. A. Olah and P. Kreienbuhl, *ibid.*, 32, 1614 (1967).
43. K. Wallenfels and W. Draber, Ber., 90, 2819 (1957).
44. G. C. Finger and C. W. Kruse, J. Am. Chem. Soc., 78, 6034 (1956).
45. D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo, and M. M. Pechet, Chem. Commun., 806 (1968).
46. T. B. Patrick and E. C. Hayward, J. Org. Chem., 39, 2120 (1974).
47. M. J. Shaw, H. H. Hyman, and R. Filler, J. Am. Chem. Soc., 92, 6498 (1970).
48. (a) I. Agranat, M. Rabinovitz, H. Selig, and C.-H. Lin, Chem. Lett., 1271 (1975); (b) *ibid.*, Experientia, 32, 417 (1976); (c) M. Zupan and A. Pollak, J. Org. Chem., 40, 3794 (1975); (d) S. P. Anand, L. A. Quarterman, P. A. Christian, H. H. Hyman, and R. Filler, *ibid.*, 3796; (e) E. D. Bergmann, H. Selig, C.-H. Lin, M. Rabinovitz, and I. Agranat, *ibid.*, 3793; (f) S. P. Anand, L. A. Quarterman, H. H. Hyman, K. G. Migliorese, and R. Filler, *ibid.*, 807; (g) S. P. Anand and R. Filler, J. Fluor. Chem., 7, 179 (1976); (h) R. Filler, L. Quarterman, N. S. Shosoo, and K. G. Migliorese, Abs. Pap. ACS, 170:14 (1975).

NUCLEOPHILIC SUBSTITUTION AT CARBON WITH ORGANOALUMINUM REAGENTS

Reported by Norman J. Peters

December 9, 1976

Organoaluminum reagents have recently emerged as useful alkylating agents in "cross-coupling" type reactions. In general, they provide an excellent alternative to Grignard¹ and organocuprate² reagents for the alkylation of tertiary, benzyl, and allyl carbons. They often effect the alkylation without the elimination and/or reduction which often occurs when Grignard or organocuprate reagents are used. Although they are pyrophoric, they can be safely handled under dry nitrogen.³ The simple trialkylaluminum reagents (methyl, ethyl, iso-butyl, and phenyl) are commercially available, while more complex reagents can be prepared from the corresponding organolithium reagent.⁴

Kennedy^{5,6} has found that tertiary alkyl, benzyl, and allyl halides can be cleanly methylated with trimethylaluminum, often in quantitative yield. Early qualitative studies⁵ indicated that the order of reactivity of halides is: 3°, allyl, benzyl > 2° > 1°. Kennedy has observed a carbonium ion-type rearrangement in this reaction⁷ and an analogous ethylation of an optically active chloride gave predominately racemization.⁸ A more detailed kinetic study of the reaction of tert-butyl halides showed that the reactivity of halides is: Cl > Br > I, and that the reaction is much faster in halomethane solvents such as chloromethane than in cyclopentane.⁸ On the basis of these observations, Kennedy has proposed an ionic mechanism⁸ and has used this reaction as a model for aluminum alkyl/alkyl halide polymerization initiator systems.^{5,8,9}

Kennedy^{5,8} and Priola and coworkers¹⁰ have studied the alkylation of some alkyl halides with triethylaluminum in halomethane solvents; however, Miller¹¹ has studied the reaction of a wider variety of alkyl halides with triethylaluminum under slightly different conditions. Miller found that triethylaluminum in the presence of a stoichiometric amount of ether effected the alkylation of benzyl halides in good yields (~70%) although the yields of other alkyl halides were less satisfactory. Kennedy has reported successful alkylations with triisobutylaluminum⁵ and triphenylaluminum.¹²

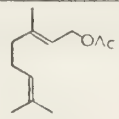
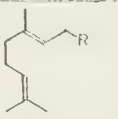
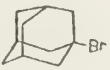
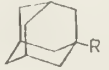
Vinyldialkylaluminum reagents can be used to alkylate allyl bromides to form 1,4-dienes in 56-70% yield.¹³ Trialkynylaluminum reagents have been shown to alkylate tertiary halides and secondary sulfonates in high yields (86-99%).¹⁴

Yamamoto^{15,16} has demonstrated that allyl (geranyl and neryl) esters, and to a lesser extent tetrahydropyranyl ethers, can be coupled with trialkylaluminum reagents or with the heteroatom ligand (X) of reagents of the type R₂AlX (X = OR, SR, or NHR). The reaction proceeded with retention of the stereochemistry of the allyl double bond and predominate formation (70-97%) of the α isomer.

Meisters and Mole^{17,18} have reported that alcohols,¹⁹ aldehydes and ketones,²⁰ and carboxylic acids²¹ can be exhaustively methylated with excess trimethylaluminum at high temperatures (100-200°) to products having mono, di, and trimethylated quaternary carbons respectively. Yields range from 40% for some aliphatic compounds to quantitative for compounds with one or more α aryl groups. Kochi²² observed that cis- and trans-4-tert-butylcyclohexanols gave the same ratio of axial and equatorial products. The pyrolysis of alkoxy diethylaluminum compounds yields predominately

elimination.²³ The photodecomposition of benzyloxydialkylaluminums has been shown²⁴ to furnish good yields (69-83%) of the α alkylated products (methyl, ethyl, and iso-butyl).

Table 1. Representative Alkylations with Organoaluminum Reagents

Compound	R in R ₃ Al	Product	Yield	Temp.	Solvent	Ref.
C ₆ H ₅ CHCH ₂ Cl	CH ₃ -	C ₆ H ₅ CH(CH ₃) ₂	100%	-78°	CH ₃ Cl	5
C ₆ H ₅ CH ₂ CH ₂ Cl	CH ₃ CH ₂ -	C ₆ H ₅ (CH ₂) ₃ CH ₃	69%	-75°	CH ₃ Cl/hexane	11
C ₆ H ₅ C(CH ₃) ₂ OH	CH ₃ -	C ₆ H ₅ C(CH ₃) ₃	95%	110°	benzene	19
	CH ₃ -		72%	0°	hexane	15
	CH ₃ CH ₂ -		53%	0°	hexane	15
	(CH ₃) ₂ CHCH ₂ -		64%	0°	hexane	15
	CH ₃ -		90%	-70°	CH ₂ Cl ₂	25
	n-C ₄ H ₉ C≡C-		96%	0°	CH ₂ Cl ₂	14

BIBLIOGRAPHY

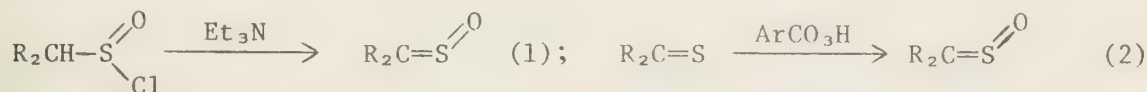
1. M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Inc., New York, N. Y., 1954.
2. G. H. Posner in "Organic Reactions," Vol. 22, John Wiley & Sons, Inc., New York, N. Y., 1975, p. 253.
3. "Handling Procedures for Aluminum Alkyl Compounds," Ethyl Corporation, Baton Rouge, La.
4. T. Mole and E. A. Jeffery, "Organoaluminum Compounds," McGraw-Hill, New York, N. Y., 1969.
5. J. P. Kennedy, J. Org. Chem., 35, 532 (1970).
6. J. P. Kennedy and S. Sivaram, *ibid.*, 38, 2262 (1973).
7. E. G. Melby and J. P. Kennedy, *ibid.*, 39, 2433 (1974).
8. J. P. Kennedy, N. V. Desai, and S. Sivaram, J. Am. Chem. Soc., 95, 6386 (1973).
9. J. P. Kennedy, Makrom. Chem., 175, 1101 (1974).
10. A. Priola, S. Cesca, and G. Ferraris, *ibid.*, 160, 41 (1972).
11. D. B. Miller, J. Org. Chem., 31, 908 (1966).
12. J. P. Kennedy and M. Ichikawa, Polym. Eng. Sci., 14, 322 (1974).
13. R. A. Lynd and G. Zweifel, Synthesis, 658 (1974).
14. E. Negishi and S. Baba, J. Am. Chem. Soc., 97, 7385 (1975).
15. S. Hashimoto, Y. Kitagawa, S. Iemura, H. Yamamoto, and H. Nozaki, Tet. Lett., 30, 2615 (1976).
16. Y. Kitagawa, S. Hashimoto, S. Iemura, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., 98, 5030 (1976).
17. A. Meisters and T. Mole, J. Chem. Soc., Chem. Commun., 16, 595 (1972).
18. E. A. Jeffery, A. Meisters, and T. Mole, Aust. J. Chem., 27, 2569 (1974).
19. D. W. Harney, A. Meisters, and T. Mole, *ibid.*, 27, 1639 (1974).
20. A. Meisters and T. Mole, *ibid.*, 27, 1655 (1974).
21. A. Meisters and T. Mole, *ibid.*, 27, 1665 (1974).
22. R. G. Salomon and J. K. Kochi, J. Org. Chem., 38, 3715 (1973).
23. C. P. Stepovik and I. A. Khamylova, Zh. Obshch. Kim., 45, 61, 54 (Eng. trans.) (1975).
24. J. Furukawa, K. Omura, O. Yamamoto, and K. Ishikawa, J. Chem. Soc., Chem. Commun., 77 (1974).
25. E. W. Della and T. K. Bradshaw, J. Org. Chem., 40, 1638 (1975).

CHEMISTRY OF SULFINES

Reported by Patrick H. W. Lau

December 13, 1976

Sulfines are heterocumulenic compounds containing the $R_2C=S=O$ system.¹ Their stability is in marked contrast to the structurally related sulfenes, $R_2C=SO_2$, which are known only as reactive intermediates.² Two common methods for generating sulfines are: elimination of hydrogen chloride from sulfinyl chlorides (eq. 1)³ and direct oxidation of thiocarbonyl compounds with peracids (eq. 2).⁴



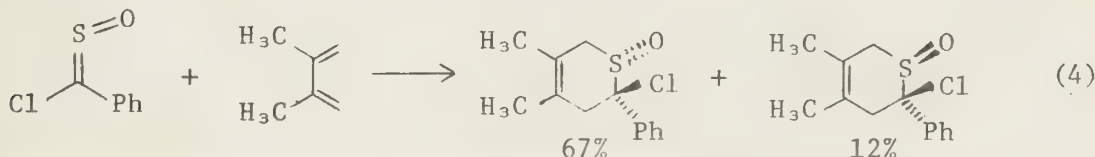
Sulfine formation by reaction of singlet oxygen with thiophene,⁵ sulfonyl chlorides with nitrogen bases,⁶ and flash vacuum pyrolysis of thietane S-oxide and 1,3-dithietane 1-oxides⁷ have been reported, but these reactions are not of general applicability.

The CSO group is bent as shown by X-ray⁸ and microwave^{7,9} experiments. The angle varies from about 104 to 115° depending on attached substituents. The two geometrical isomers can be distinguished by dipole moment measurements^{4e,6c} or by nmr analysis and with the use of shift reagents.^{4e,10}

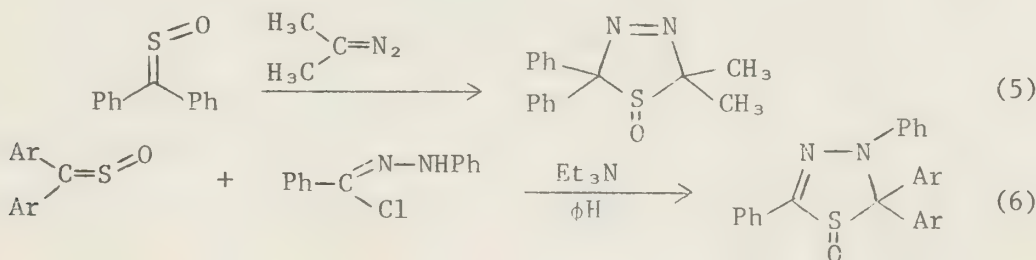
The oxygen atom of some sulfines can be removed by treatment with triphenylphosphine¹¹ or diiron enneacarbonyl.¹² Alkyl and arylsulfines react with chlorine to give the corresponding α -chloro sulfinyl chlorides.^{3a,11} Oxathiirans have been proposed as unstable intermediates in the photolysis of sulfines to the corresponding carbonyl compounds.¹³ Reaction with nucleophiles such as methyl lithium (eq. 3),¹⁴ benzenethiolate,^{4d} cyanide,¹⁵ and benzenesulfinate¹⁵ provide products arising from an initial attack of the nucleophile at the sulfur atom of the sulfine.



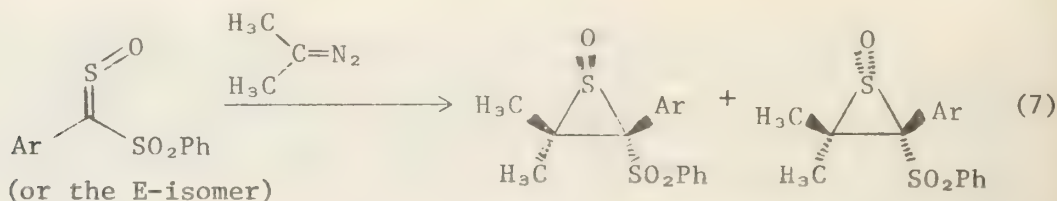
Similarly, electrophilic alkylation of thiocamphor S-oxide in the presence of thallium ethoxide with active alkyl halides also occurs at sulfur.¹⁶ Diels-Alder reactions with 1,3 dienes result in six-membered ring sulfoxides in which the configuration of the starting sulfines is predominantly retained (eq. 4).^{4c,11,17}



With 1,3-dipoles such as diazoalkanes (eq. 5)^{4f,18} and nitrilimines (eq. 6),¹⁹ Δ^3 - and Δ^2 -1,3,4-thiadiazoline-S-oxides are formed, respectively.



Alternatively, reaction of sulfines with diazoalkanes may lead to epi-sulfoxides in a stepwise process when bulky substituents are introduced in either of the reactants (eq. 7).^{4f,18c,20}



BIBLIOGRAPHY

1. For a review on sulfines: B. Zwanenburg and J. Strating, *Quart. Reports on Sulfur Chem.*, 5, 79 (1970).
2. G. Opitz, *Angew. Chem. Int. Ed. Engl.*, 6, 107 (1967).
3. (a) W. A. Sheppard and J. Diekmann, *J. Am. Chem. Soc.*, 86, 1891 (1964); (b) J. Strating, L. Thijs, and B. Zwanenburg, *Rec. Trav. Chim. Pays-Bas*, 83, 631 (1964).
4. (a) J. Strating, L. Thijs, and B. Zwanenburg, *Tetrahedron Lett.*, 65 (1966); (b) B. Zwanenburg, L. Thijs, and J. Strating, *Rec. Trav. Chim. Pays-Bas*, 86, 577 (1967); (c) *Idem*, *Tetrahedron Lett.*, 4461 (1969); (d) *Idem*, *Rec. Trav. Chim. Pays-Bas*, 89, 687 (1970); (e) *Idem*, *ibid.*, 90, 614 (1971); (f) B. Zwanenburg, A. Wagenaar, L. Thijs, and J. Strating, *J. Chem. Soc. Perkin I*, 73 (1973).
5. (a) C. N. Skold and R. H. Schlessinger, *Tetrahedron Lett.*, 791 (1970); (b) H. H. Wasserman and W. Strenthlow, *ibid.*, 795 (1970).
6. (a) E. Wedekind, D. Schenck, and R. Stüsser, *Chem. Ber.*, 56, 633 (1923); (b) J. F. King and T. Durst, *Tetrahedron Lett.*, 585 (1963); (c) *Idem*, *J. Am. Chem. Soc.*, 85, 2676 (1963); (d) J. Strating, *Rec. Trav. Chim. Pays-Bas*, 83, 95 (1964); (e) J. F. King and T. Durst, *Can. J. Chem.*, 44, 819 (1966).
7. E. Block, R. E. Penn, R. J. Olsen, and P. F. Sherwin, *J. Am. Chem. Soc.*, 98, 1264 (1976).
8. (a) T. W. Hummelink, *J. Cryst. Mol. Struct.*, 4, 87 (1974) and references cited therein; (b) T. W. Hummelink, *ibid.*, 4, 373 (1974).
9. R. E. Penn and R. J. Olsen, *J. Mol. Spec.*, 61, 21 (1976).
10. A. Tangerman and B. Zwanenburg, *Tetrahedron Lett.*, 79 (1973).
11. J. Strating, L. Thijs, and B. Zwanenburg, *Rec. Trav. Chim. Pays-Bas*, 86, 641 (1967).
12. H. Alper, *J. Organometal. Chem.*, 84, 347 (1975).
13. L. Carlsen, N. Harrit, and A. Holm, *J. Chem. Soc. Perkin I*, 1404 (1976) and references cited therein.
14. A. G. Schultz and R. H. Schlessinger, *J. Chem. Soc. Chem. Commun.*, 747, 748 (1970).
15. G. E. Veenstra and B. Zwanenburg, *Rec. Trav. Chim. Pays-Bas*, 95, 28 (1976).
16. G. E. Veenstra and B. Zwanenburg, *Rec. Trav. Chim. Pays-Bas*, 95, 37 (1976).
17. B. Zwanenburg, L. Thijs, J. B. Brones, and J. Strating, *Rec. Trav. Chim. Pays-Bas*, 91, 443 (1972).
18. (a) B. F. Bonini, G. Maccagnani, A. Wagenaar, L. Thijs, and B. Zwanenburg, *J. Chem. Soc. Perkin I*, 2490 (1972); (b) C. G. Venier and C. G. Gibbs, *Tetrahedron Lett.*, 2293 (1972); (c) L. Thijs, A. Wagenaar, E. M. M. Van Rens, and B. Zwanenburg, *Tetrahedron Lett.*, 3589 (1973).
19. B. F. Bonini, G. Maccagnani, L. Thijs, and B. Zwanenburg, *Tetrahedron Lett.*, 3569 (1973).
20. B. F. Bonini, A. Cappelli, G. Maccagnani, and G. Mazzanti, *Gazz. Chim. Ital.*, 105, 827 (1975).

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ORGANIC SEMINAR ABSTRACTS

1976-77

SEMESTER II

School of Chemical Sciences
Department of Chemistry
University of Illinois
Urbana, Illinois
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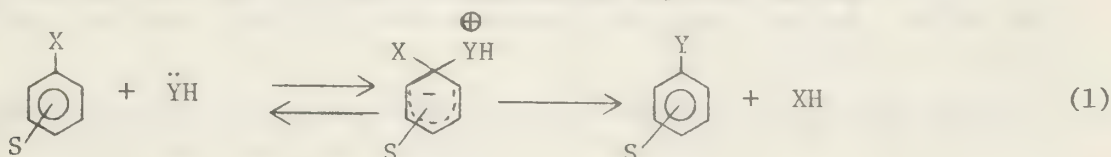
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BASE CATALYSTS IN THE ADDITION-ELIMINATION MECHANISM OF AROMATIC
NUCLEOPHILIC SUBSTITUTION WITH AMINES

Reported by Susan Ruth Krauss

January 27, 1977

Nucleophilic aromatic substitution reactions involving substrates activated by electron-withdrawing substituents are generally believed to proceed by the addition-elimination mechanism depicted in Eq. 1.



The multi-step nature of this reaction is supported by several lines of evidence. Prominent among these is the occurrence and form of base catalysis by primary and secondary amines which has been observed in some of these reactions. This seminar will examine base catalysis in nucleophilic substitution reactions of activated benzenoid derivatives with primary and secondary amines, with the objective of analyzing the various factors which determine whether or not a given system will exhibit catalysis.

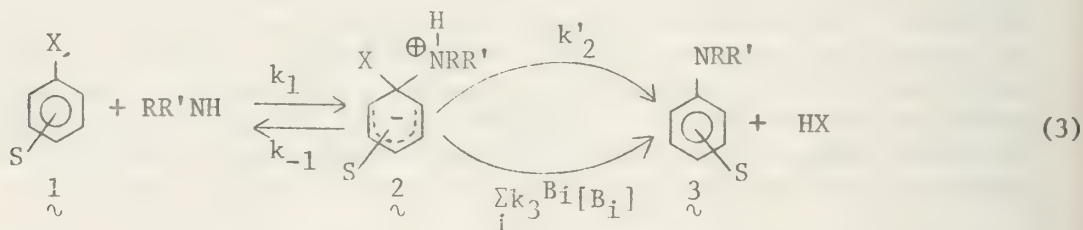
Historical. The case for the intermediate complex has been extensively reviewed.¹ It comprises the following principal arguments:² (1) Certain highly activated substrates have been observed to form stable, isolable complexes similar to the intermediate complex in Eq. 1. (2) In reactions known to involve breaking of the carbon-halogen bond in the rate-determining step, the carbon-fluoride bond is broken very much slower than the other carbon-halogen bonds. However, in many nucleophilic substitution reactions of activated halobenzenes the observed order of mobility of the halogens is $F \gg Cl \sim Br \sim I$. It is therefore concluded that in such reactions the C-X bond is not broken in the rate-determining step. (3) In reactions of piperidine with several 1-X-2,4-dinitrobenzenes, six substituents with first atoms representing five elements were displaced at nearly the same rate, and both the enthalpy and entropy of activation were found to be constant within the series.³ Since there are ordinarily great differences in the rates of heterolysis of different bonds, the similarity of rates observed indicates that little or no breaking of the C-X bond has occurred in the rate-determining transition state. There has been some recent discussion of the "absence of element effect" criterion for assessing whether or not bond-breaking occurs during the rate-determining step of nucleophilic substitution reactions.⁴ (4) A number of base catalyzed nucleophilic substitution reactions of amines with activated aromatic substrates show a rate dependence on base concentration that is linear but levels off at high base concentrations. This behavior is indicative of a change in the rate-determining step, which requires that there be an intermediate on the reaction pathway, and that the formation and decomposition of the intermediate have different sensitivities to catalysis. (5) The transition states and intermediate for the two-step mechanism are easily rationalized quantum mechanically, while the transition state for a one-step mechanism is difficult to rationalize.

Kinetics. Reactions described as base catalyzed are those in which the experimental second-order rate coefficient, k_A (first-order in substrate, first order in amine), has been found to be augmented by increase in amine concentration or by the addition of other bases. Most of the systems which exhibit base catalysis can be accommodated empirically by Eq. 2,

$$k_A = k' + k'' [B] \quad (2)$$

in which k' is the rate coefficient for the uncatalyzed reaction, k'' is that for the catalyzed reaction and B is the base catalyst. Bunnett and Garst⁵ suggested that the observed cases of catalysis could be broadly divided into two categories, classified in terms of the relative rates of the catalyzed and uncatalyzed reactions at 1 M base concentration. The first category contains those systems showing strong catalysis with k''/k' greater than 50 M^{-1} . The second category contains systems exhibiting mild catalysis for which this ratio is less than 5 M^{-1} .

The mechanism depicted in Eq. 3 is the simplest of those proposed, and most of the kinetic data in the literature have been analyzed in terms of it.



The various bases, B_i , are typically the lyate ion, tertiary amines, the nucleophile itself, or others which may be specifically added to the reaction mixture. Since in the study of base catalysis the concentrations of all the bases except one, B_j , are generally held constant, k_2 will be taken to represent the true uncatalyzed rate coefficient k'_2 plus the sum of all the $k_3^{B_i}[B_i]$ terms for which the base concentration is held constant.

Applying the steady-state approximation to the reaction depicted in Eq. 3 leads to the following equation:

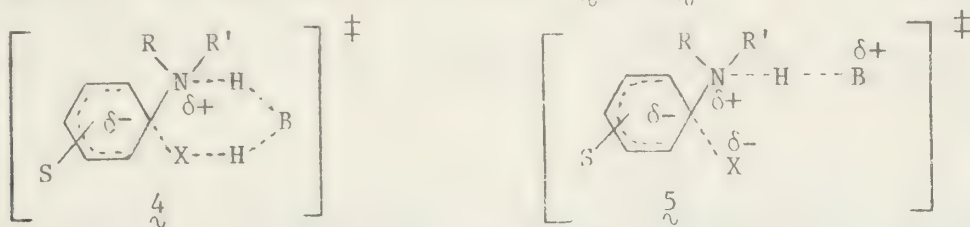
$$\frac{\text{rate}}{[1][RR'NH]} = k_A = \frac{k_1k_2 + k_1k_3^{B_j}[B_j]}{k_{-1} + k_2 + k_3^{B_j}[B_j]} \quad (4)$$

Provided that $k_2 \ll k_{-1}$, Eq. 4 in principle describes a dependence of k_A on $[B_j]$ which is linear at low concentrations but becomes curved and finally levels off as the base concentration is increased.⁶

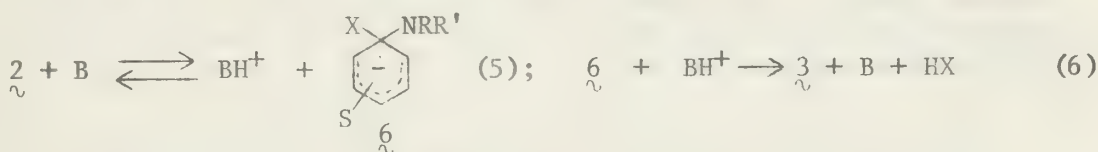
It has not been possible from steady-state kinetics to elucidate in detail how a base catalyzes the expulsion of the leaving group X from intermediate 2. The reactions are studied under pseudo first-order conditions employing excess amine and monitoring the reaction by photometric analyses of aliquots withdrawn at fixed intervals. Employing this technique, numerous reactions have been studied and a large amount of information regarding the effects of solvent, leaving group, and nucleophile has been gathered. Although the kinetic data are interpreted in terms of a two step mechanism, this is not meant to imply that the reaction represented by k_3 is necessarily a one step process but rather that Eq. 4 is the simplest equation consistent with the observed kinetics. More involved experimental techniques are necessary to probe the mechanism of the k_3 step.

The conversion of the intermediate 2 to the product 3 involves the removal of a proton from nitrogen and the breaking of the bond to the leaving

group. In the base catalyzed pathway k_3 , these two events may occur in a single, concerted process. Two possible transition states consistent with such a process are depicted in structures $\tilde{4}$ and $\tilde{5}$.



Alternatively, the k_3 pathway could involve a two step process illustrated in Eqs. 5 and 6.



The reactions of 2,4-dinitro-1-naphthyl ethyl ether with n-butyl- and tert-butylamine in dimethyl sulfoxide solution were studied by stopped-flow uv-visible spectroscopy. Both reactions were shown to be consistent with the k_3 pathway depicted in Eqs. 5 and 6. An intermediate was observed, and its composition was demonstrated to be that of $\tilde{6}$. In these two reactions, the formation of intermediate $\tilde{6}$ was not base catalyzed. Its transformation to product $\tilde{3}$, the rate determining step, was first order in butylammonium ion but independent of amine concentration.

Solvent. In polar, protic solvents facilitating C-X bond cleavage, strong base catalysis is not observed. In less polar, aprotic solvents, catalysis is observed in substrates with poor leaving groups. This is illustrated by the reaction of aniline with 1-fluoro- and 1-chloro-2,4-dinitrobenzene (Table 1 and Figure 1).

Table 1. The Reaction of 1-X-2,4-Dinitrobenzene with Aniline at 50° C

X	Solvent	Base Catalysis by Aniline	$k_A, 10^4 \text{ M}^{-1} \text{ sec}^{-1}$	Ref.
F	EtOH	No	168	8
Cl	EtOH	No	2.69	8
Cl	Acetone	No	0.439	9
F	Acetone	Yes	Sec Figure 1	9

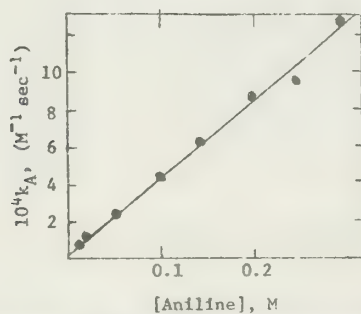


Figure 1. Reaction of FDNB with aniline catalyzed by aniline in acetone at 50° C.

For the reaction of aniline with 1-fluoro-2,4-dinitrobenzene (FDNB) in acetone, the second step is rate-determining with the base catalyzed pathway favored (the ratio of the catalyzed to uncatalyzed rate constants, k_3^{Aniline}/k_2 , is about 200 M^{-1}). A similar study was done with different solvents.¹⁰

Leaving Group. The leaving group capability (nucleofugicity) has been recognized to decrease with increasing pK_a of the conjugate acid of the leaving group.¹¹ The expectation that base catalysis should increase as the leaving group is less prone to separate from carbon is supported by the data appearing in Table 2.¹² The ratio k_3^{NaOH}/k_2 is a measure of the effectiveness of base catalysis.

Table 2. The Reactions of 1-Substituted-2,4-dinitrobenzenes with Piperidine in 10% Dioxane-90% Water at 29.4°C Subject to Catalysis by NaOH

Leaving Group	pK_a	$k_3^{\text{NaOH}}/k_2 \text{ (M}^{-1}\text{)}$
2,4-Dinitrophenoxy	4.09	---
4-Nitrophenoxy	7.14	≈ 25
Thiophenoxy	6.52	43.6
Phenoxy	10	1750
Methoxy	c. 16.7	2.5×10^5

The mathematical basis of this expectation can be shown with reference to Eq. 4. When the leaving group is a good one, such as 2,4-dinitrophenoxide, the condition of $\{k_2 + k_3^{\text{Bj}}[\text{B}_j]\} \gg k_{-1}$ exists and Eq. 4 simplifies to Eq. 7. A plot of k_A vs. $[\text{NaOH}]$ (Figure 2) is nearly flat as called for by Eq. 7. Phenoxide is a moderately good leaving group, and its kinetic data describe a curved dependence of k_A on $[\text{NaOH}]$ as illustrated in Figure 3. At low base concentrations, $k_{-1} \gg \{k_2 + k_3^{\text{Bj}}[\text{B}_j]\}$ and Eq. 4 is simplified to Eq. 8. As the base concentration is increased, the dependence of k_A on $[\text{NaOH}]$ becomes curved and finally levels off at high concentrations where Eq. 7 prevails. A poor leaving group is exemplified by methoxide and its plot of k_A vs. $[\text{NaOH}]$ exhibits less tendency to flatten out at higher base concentrations (Figure 4). One must go to relatively high base concentrations in order to see the horizontal part of the graph where Eq. 4 simplifies to Eq. 7.

$$k_A = k_1 \quad (7); \quad k_A = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3^{\text{Bj}}[\text{B}_j]}{k_{-1}} \quad (8)$$

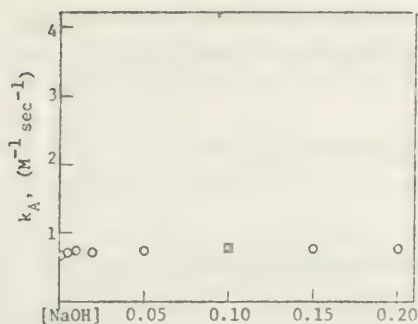


Figure 2. Reaction of bis(2,4-dinitrophenyl) ether with piperidine, catalyzed by NaOH.

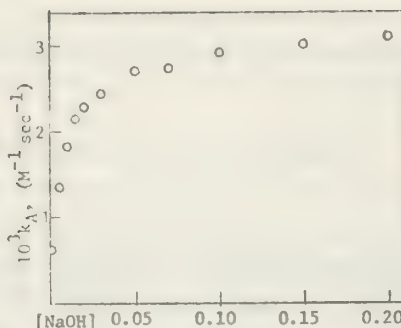


Figure 3. Reaction of 2,4-dinitrophenyl phenyl ether with piperidine, catalyzed by NaOH.

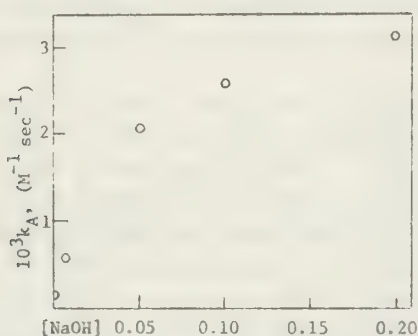


Figure 4. Reaction of 2,4-dinitroanisole with piperidine, catalyzed by NaOH.

Similar studies were done with the same systems in 60% dioxane-40% water.¹³

When BH is a weaker acid than XH, there is no driving force for the general acid catalyzed leaving group expulsion illustrated in Eq. 6.¹⁴ In such a case, the slow step becomes dissociation of intermediate 6, which amounts to an overall specific base catalysis.¹⁵

Nucleophiles. The reactions of FDNB and CDNB with sec-butyl-, n-butyl-, and tert-butylamine in benzene were studied to see if the rate of the reaction was affected by the steric bulk of the nucleophile.¹⁶ None of the reactions of CDNB was subject to base catalysis by the nucleophile, while all those of FDNB were. The relative reactivity of the fluoro and chloro substrates with the butylamines can be calculated as the ratio of the amine uncatalyzed second-order rate coefficients for the two reactions (which in the case of FDNB are given by the second-order rate coefficients extrapolated to zero nucleophile concentration). The ratios obtained were 400, 1800, and 1000 for n-butyl-, sec-butyl-, and tert-butylamine, respectively, indicating that the relative reactivities of FDNB and CDNB do not greatly depend on the steric bulk of the amine. A similar study was done with substituted piperidines.¹⁷

The nucleophilicity of the amine towards the aromatic substrate is somewhat related to the basicity of the nucleophile. In the series of secondary amines, piperidine, N-methylbenzylamine, and morpholine, k_1 decreases monotonically with decreasing basicity, but a plot of $\log k_1$ vs. pK_a is not quite linear.¹⁸

The reactions of a series of amines with FDNB and CDNB in acetonitrile¹⁹ and the reactions of FDNB and CDNB with substituted anilines¹⁰ and substituted N-methylanilines²⁰ in methanol and acetonitrile were also studied.

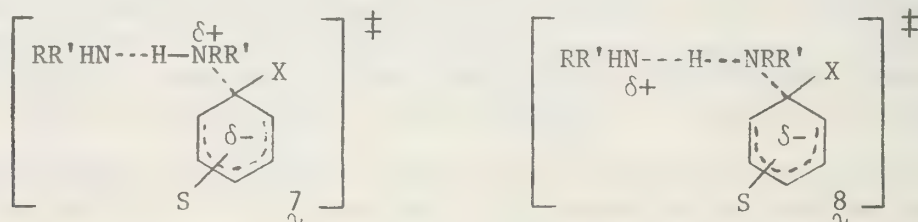
Influence of the o-Nitro Group. Bernasconi⁶ observed that the ratios k_2/k_{-1} and k_3^{Bj}/k_{-1} are considerably higher for primary amines than for secondary amines of comparable basicity in otherwise identical reactions. These empirical observations manifest themselves experimentally in that a number of reactions with secondary amines are base catalyzed ($k_2/k_{-1} \ll 1$), whereas the same reactions using primary amines are not ($k_2/k_{-1} \gg 1$). Practically all rate data which permit a comparison of these ratios for primary and secondary amines involve substrates with an o-nitro group.

Bunnett and Garst suggested that steric compression between the secondary amine and the o-nitro group in the intermediate was responsible for these observations.⁵ Bernasconi and de Rossi²¹ explained these observations based on intramolecular hydrogen bonding in the intermediate ζ .

Pietra and Cima²² studied the reactions of piperidine with 2- and 4-nitro-1-fluorobenzene in benzene. The latter was strongly catalyzed, being third order overall ($k' = 0$). The former was mildly catalyzed with k''/k' equal to 0.57 M^{-1} . These results were interpreted in terms of the transition state of the k_2 step being stabilized by the o-nitro group, with the o-nitro group assisting elimination of the ammonium proton and fluoride ion.

Weak Catalysis. Up until now, we have been discussing systems that exhibit strong catalysis. Reactions which exhibit mild catalysis have the mathematical form appropriate for base catalysis, but it is not clear whether the description of the acceleration as base catalysis is chemically warranted. There is little or no correlation between the base strength of the catalyst and its ability to increase the rate of the reaction. This observation is in contrast to the behavior exhibited by strongly catalyzed reactions. In reactions which exhibit strong catalysis, the base catalyzed pathway is more prevalent (larger k_3^{Bj}/k_2 value) when the catalyst, B_j , is OH^- as compared to the amine nucleophile. Mildly accelerated reactions show no sign of approaching a limiting value of k_A at high base concentrations. Similar accelerating effects are exhibited by nitro compounds, sulfoxides, and sulfones which do not normally display basic character in polar solvents.⁵ Most examples of weak catalysis occur in polar solvents and usually with good leaving groups. Some researchers refer to these mild accelerations as medium effects of an unknown origin. Ross²³ and Bunnett and Garst⁵ identified this mild catalysis as occurring in the first step.

Catalysis in the first step may be envisioned as occurring through a transition state such as ζ or δ to yield intermediates ζ and δ , respectively.



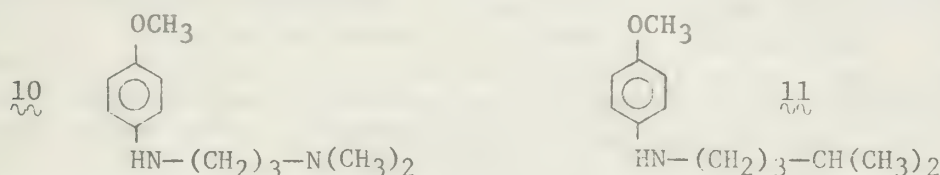
This need not necessarily involve a termolecular collision, since the k_1 step may be preceded by the fast equilibrium depicted in Eq. 9 to form the hydrogen-bonded complex ζ which would be a better nucleophile than the

amine itself. The second amine molecule in structures 7, 8 and 9 could easily be replaced by another species capable of forming a hydrogen bond with the ammonium proton.



Bifunctional Catalysis. The reactions of FDNB and CDNB with piperidine in benzene were studied in the presence of various potential catalysts.²⁴ The reaction with CDNB were not subject to catalysis. These results suggest bifunctional catalysis by α -pyridone with the catalysts supplying both nucleophilic assistance to remove the proton and electrophilic aid in separating the leaving group.

The reactions of amines 10 and 11 with CDNB, FDNB, and 1-bromo-2,4-dinitrobenzene (BDNB) with and without 1,4-diaza-bicyclo[2.2.2]octane (DABCO) as an added catalyst were studied.²⁵



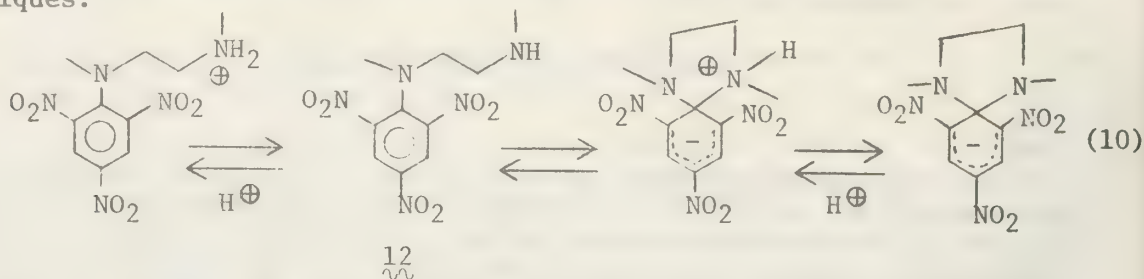
With 10, the fluorine compound was found to react much faster than the two other halogen compounds. This is in contrast to the reactions of 11, where fluoride as the leaving group gives the slowest reaction, indicating a rate limiting second step. None of the reactions with CDNB or BDNB was catalyzed by DABCO. The reaction of 11 with FDNB was catalyzed by DABCO, but the same reaction with 10 was not catalyzed. These results indicate that the diamine nucleophile can intramolecularly catalyze the reaction.

The reactions of 1,3-diaminopropane and 1,3-diamino-2,2-dimethylpropane with 2,4-dinitroanisole in benzene were studied.²⁶ The two geminal methyl groups were expected to favor a spatial arrangement in which the two amino groups would be close together, thus favoring intramolecular catalysis in the step leading to product formation. The expectation that k''/k' should be smaller for the dimethyl-substituted diamine was not observed. A similar study was done on the reactions of 1,2-diaminoethane and 1,3-diaminopropane with CDNB in methanol and with 1-phenoxy-2,4-dinitrobenzene in 60% aqueous dioxane.²⁷

The reaction of CDNB with n-butylamine proceeded more rapidly than that with benzamidine, neither reaction being subject to base catalysis by the respective nucleophiles.²⁸ Halogen substitution of 4-fluoro-1,6-dinitronaphthalene in chlorobenzene is second-order in n-butylamine and first order in benzamidine. The reaction with benzamidine is faster than that with n-butylamine. These results were interpreted to indicate that benzamidine may react bifunctionally when the k_2 step is rate limiting.

The dependence of reaction rate of piperidine with FDNB in benzene on the concentration of several added para-substituted phenols was analyzed.²⁹ The catalytic coefficients for the phenols are, within experimental error, independent of the acid strength of the catalyst. This observation is consistent with a transition state for the k_3 step in which the phenol acts as a bifunctional catalyst, thus avoiding charge accumulation on the phenol.

Rate Limiting Proton Transfer. The intramolecular Meisenheimer formation of N,N'-dimethyl-N-picrylethylenediamine (12), Eq. 10, was studied as a function of pH and buffer concentration using temperature-jump uv spectroscopy techniques.³⁰



The results suggest that reactions involving weakly basic nucleophiles or poorly activated substrates may exhibit base catalysis which is due to rate-limiting proton transfer in the k_3 step. Related work with other Meisenheimer systems substantiates this conclusion.³¹

Isotope Studies. The reaction of 2,4-dinitrophenyl phenyl ether with piperidine in 40%-water-60%-dioxane was studied for kinetic oxygen isotope effect.³² The reaction is strongly catalyzed by hydroxide ion. A primary isotope effect is observed which decreases with increasing sodium hydroxide concentration. This is expected because as the base concentration increases, the overall rate becomes increasingly dependent on the first step.

A number of systems were studied for kinetic isotope effects by substituting deuterium for hydrogen on the amino group of the nucleophile.^{1,6,23} Some of the work was repeated by several research groups with conflicting results. In those cases where an isotope effect was observed, it was a small one. These results seem to indicate that in some reactions, the N-H bond is not broken in the rate-determining step, or that the isotope effect is being masked. Substitution of deuterium for hydrogen does not, in general, have a large effect on the energetics of hydrogen bonding.^{1c} The absence of an isotope effect may be in accord with Swain's "solvation rule" which predicts that a proton being transferred from one nitrogen (or oxygen) to another should lie in an entirely stable potential at the transition state, and hence, no primary isotope effect should be observed.³³

As a practical extension of these studies, Bunnett and Hermann³⁴ looked at the kinetics of the reactions of FDNB and 2,4-dinitrophenyl phenyl ether with several amino acids in several solvents to see if pH variations might enable selective dinitrophenylation of certain aminoacyl moieties. The most useful observation of these experiments was that the reaction rates seem to be increased in media containing high percentages of dimethylsulfoxide.

Conclusion. Nucleophilic aromatic substitution reactions with amines exhibit two types of base catalysis. Strong catalysis, which occurs in reactions with substrates having poor leaving groups and usually in an aprotic, mildly polar solvent, is believed to occur in the product-forming step. In these systems, it is possible to observe a change in the rate limiting step, with product formation being rate limiting at low catalyst concentration and intermediate formation being rate limiting at high catalyst concentration. Reactions with substrates having good leaving groups often exhibit weak catalysis, believed to occur in the first step, and these reactions do not reach a limiting rate at high catalyst concentration. The exact mechanism of the catalysis is not clearly defined in all the reactions.

BIBLIOGRAPHY

1. (a) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968; (b) Th. J. de Boer and I. P. Dirkx in "The Chemistry of the Nitro and Nitroso Groups," Part 1, H. Feurer, Ed., Interscience, New York, N. Y., 1969, pp. 487-612; (c) S. D. Ross, *Progr. Phys. Org. Chem.*, 1, 31-74 (1963); (d) F. Pietra, *Quart. Rev., Chem. Soc.*, 23, 504-521 (1969).
2. J. F. Bunnett and J. J. Randall, *J. Am. Chem. Soc.*, 80, 6020-6030 (1958).
3. J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *ibid.*, 79, 385-391 (1957).
4. (a) B. Lamm and J. Lammert, *Acta. Chem. Scand.*, 27, 191-196 (1973); (b) Z. Rappoport and J. F. Bunnett, *Acta. Chem. Scand. B.*, 28, 478-479 (1974).
5. J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, 87, 3875-3878 (1965).
6. C. F. Bernasconi, *MTP Int. Rev. Sci., Org. Chem. Ser. One*, 3, 33-63 (1973).
7. J. A. Orvik and J. F. Bunnett, *ibid.*, 92, 2417-2426 (1970).
8. N. B. Chapman and R. E. Parker, *J. Chem. Soc.*, 3301-3307 (1951).
9. R. H. de Rossi and R. A. Rossi, *J. Org. Chem.*, 39, 3486-3488 (1974).
10. (a) J. Kavalek, J. Haasova, and V. Sterba, *Collec. Czech. Chem. Commun.*, 37, 3333-3338 (1972); (b) J. Kavalek and V. Sterba, *ibid.*, 38, 884-891 (1973).
11. A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, 87, 3209-3216 (1965).
12. J. F. Bunnett and C. F. Bernasconi, *ibid.*, 87, 5209-5218 (1965).
13. J. F. Bunnett and C. F. Bernasconi, *J. Org. Chem.*, 35, 70-75 (1970).
14. C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, 38, 500-506 (1973).
15. W. P. Jencks, *J. Am. Chem. Soc.*, 94, 4731-4732 (1972).
16. F. Pietra and D. Vitali, *J. Chem. Soc. B*, 1200-1203 (1968).
17. F. Pietra and F. D. Cima, *Tetrahedron Lett.*, 1925-1931 (1966).
18. C. F. Bernasconi, *J. Org. Chem.*, 32, 2947-2952 (1967).
19. D. Ayediran, T. O. Bamkole, and J. Hirst, *J. Chem. Soc. Perkin Trans. 2*, 1396-1398 (1976).
20. J. Kavalek, J. Kubias, and V. Sterba, *Collec. Czech. Chem. Commun.*, 37, 4041-4045 (1972).
21. C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, 41, 44-49 (1976).
22. F. Pietra and D. Vitali, *Tetrahedron Lett.*, 4573-4577 (1967).
23. S. D. Ross in "Comprehensive Chemical Kinetics," 13, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, The Netherlands, 1972, 406-431.
24. F. Pietra and D. Vitali, *Tetrahedron Lett.*, 5701-5706 (1966).
25. B. Lamm and I. Palmertz, *Acta. Chem. Scand. B.*, 30, 15-20 (1976).
26. B. Lamm and I. Palmertz, *ibid.*, 30, 21-23 (1976).
27. H. H. Lee and L. Main, *Aust. J. Chem.*, 28, 2521-2526 (1975).
28. G. Biggi, F. D. Cima, and F. Pietra, *J. Chem. Soc. Perkin Trans. 2*, 188-192 (1972).
29. F. Pietra and D. Vitali, *J. Chem. Soc. B*, 1318-1321 (1968).
30. C. F. Bernasconi and C. L. Gehriger, *J. Am. Chem. Soc.*, 96, 1092-1099 (1974).
31. (a) S. Sekiguchi and K. Okada, *J. Org. Chem.*, 40, 2782-2786 (1975); (b) C. F. Bernasconi and F. Terrier, *J. Am. Chem. Soc.*, 97, 7458-7466 (1975); (c) C. F. Bernasconi, R. H. de Rossi, and C. L. Gehriger, *J. Org. Chem.*, 38, 2838-2842 (1973); (d) C. F. Bernasconi and H. S. Cross, *ibid.*, 39, 1054-1058 (1974); (e) C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, *J. Am. Chem. Soc.*, 98, 8451-8459 (1976).
32. C. R. Hart and A. N. Bourns, *Tetrahedron Lett.*, 2995-3002 (1966).
33. C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, 87, 1553-1561 (1965).
34. J. F. Bunnett and D. H. Hermann, *Biochemistry*, 816-822 (1970).

STEREOCHEMICAL CONTROL IN ELECTROORGANIC SYNTHESIS:
THE ROLE OF ADSORPTION AND THE DOUBLE LAYER

Reported by Keith A. Horn

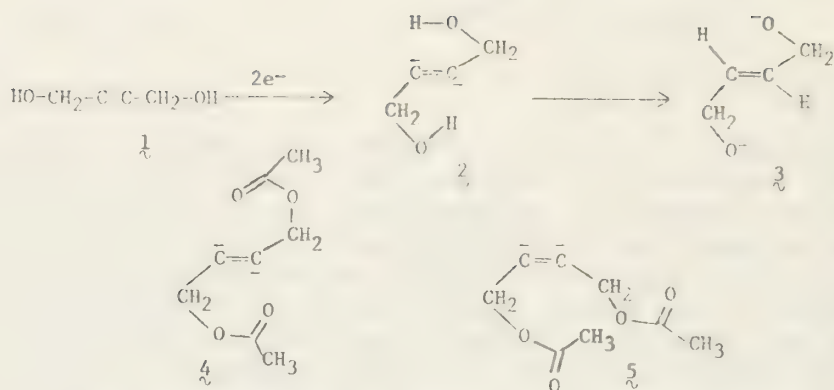
January 31, 1977

Introduction. All electroorganic reactions are solution-electrode interface reactions, i.e. the electron transfer steps of electroorganic syntheses are necessarily heterogeneous processes occurring directly at or within a few angstroms of the electrode surface. This region in which electron transfer occurs is a highly structured region called the electrical double layer.¹ The double layer consists of a complex ordering of solvent, substrate and electrolyte molecules and ions^{2a,b} extending at most 3000 Å (generally < 100 Å) into the bulk of the solution.^{3a,b} The heterogeneous nature of electroorganic reactions, while producing complex reaction pathways and making reaction mechanism studies difficult, yields the exciting possibility of carrying out highly stereospecific and stereoselective reactions. This seminar will present those studies of electroorganic reactions whose stereochemical course is determined by specific adsorption on the electrode surface or by the heterogeneous nature of the electrical double layer.

1. Reductions. In the last 15 years, there has been a surge of interest in the application of stereochemical analysis to the understanding of the mechanism of electroorganic reactions. Two reviews in this area have dealt with some aspects of the stereochemical control of cathodic processes.^{4a,b}

Acetylenes → Alkenes. In 1943, Campbell and Young found that 5-decyne, 4-octyne and diphenylacetylene could be reduced at a spongy nickel cathode in acidic ethanol to the pure cis olefins in 75-80% yields.⁵ Analogy was made to catalytic hydrogenation.^{6a,b} Through the use of various metal cathodes, evidence was obtained to show that this was a surface controlled reaction. No reduction of 5-decyne could be obtained with spongy cadmium, lead, or mercury cathodes, while spongy copper electrodes produced only low yields of the cis-5-decene. More recently it has been established that the reduction of acetylenes at Ag-Pd alloy cathodes yields exclusively the thermodynamically less stable cis olefins in good yield.⁷ On all cathodes of low hydrogen overpotential (Pt, Ni, Ag-Pd), the reduction proceeds via reaction of the adsorbed acetylene with adsorbed hydrogen atoms.⁸ Polarographic data⁸ and the production of diphenylfumaric acid during the reduction of diphenylacetylene in the presence of CO₂⁹ have shown that on mercury and electrodes of high hydrogen overpotential, the reduction of acetylenes occurs by a direct reduction involving radical anions or dianionic intermediates. The reduction of but-2-yn-1,4-diol on mercury in methanol/TMAC produces only the trans-but-2-en-1,4-diol, while the corresponding diacetate produces a 59.5/40.5 trans-cis mixture of the but-2-ene-1,4-diacetate.¹⁰ This was interpreted in terms of the adsorbed dianionic intermediates as shown in Figure 1. An intramolecular proton transfer mechanism was suggested to account for the stereochemistry of the reduction of the 1,4-diol (2), while the adsorbed conformations (4 and 5) of the dianion from the diacetate would both readily lead to the product alkene.

Figure 1



Reduction of Ketones. Electrochemical reduction of ketones leads both to carbinols and pinacols.¹¹ Though a number of reports of pinacolizations which yielded only one of the possible diastereomers^{12a,b,c} might suggest adsorption control of stereochemistry, a series of experiments by Stocker and Jenevein *et al.*^{13a-d} showed that the intermediate ketyl radicals react free in solution to form pinacols, the diastereomeric ratio depending on inter and intra species hydrogen bonding. The evidence consisted of the similar meso/dl pinacol ratios obtained from the photochemical and electrochemical reductions of acetophenone under a wide variety of solution and electrode compositions. There is some conflicting evidence from recent steady state, potentiodynamic and potential step kinetic studies.¹⁴ Two exceptions have been reported. The first is the pinacolization of benzaldehyde. In the presence of specifically adsorbed ions (tetraethylammonium and iodide), the dl/meso product pinacol ratio changed from 1.19 to as low as 0.48, while the homogeneous photochemical dl/meso ratio was unaffected by these same ions.¹⁵ These data indicate that the reaction occurs at the solution-electrode interface. Second, recently it has been suggested that the cis-trans ratios of the products of the intramolecular pinacolizations of 2,2'-dibenzoylbiphenyl and 1,8-dibenzoylnaphthalene are controlled by specific adsorption of radical intermediates.¹⁶ The possibility of surface reactions has also been suggested in the enantioselective and stereoselective pinacolization of tricyclic α,β -unsaturated ketones.¹⁷

Much more evidence, however, has accumulated to implicate adsorbed species in the formation of carbinols from ketones. The surface nature of the reaction was pointed out by the early work of Cornubert *et al.*¹⁸ They found that reduction of 2-methylcyclohexanone gave pure trans-2-methylcyclohexanol at Pb or Hg cathodes, a mixture of cis- and trans-2-methylcyclohexanol (trans predominant) at a Ni cathode, and pure cis-2-methylcyclohexanol at a Cu cathode.

The electrochemical reduction of α -methyldeoxybenzoin was found to yield the pure erythro alcohol.¹⁹ These results were rationalized in terms of adsorption of the intermediate ketyl radical, possibly through a covalent bond with the mercury electrode.

Shono and Mitani²⁰ have suggested that in sulfuric acid/methanol solution, the intermediate anion in the reduction of alkyl substituted cyclohexanones is protonated in the double layer and the stereochemistry is controlled through steric interaction with the electrode. In isopropanol, the intermediate carbanion diffuses into solution where it may invert prior to protonation. The stereochemical course of the electrochemical reduction of the conformationally locked 4-*t*-butylcyclohexanone has also been interpreted in terms of

the rate of protonation of the carbanion formed from cleavage of an intermediate-electrode complex.^{21a,b} (See Figure 2.)

Figure 2



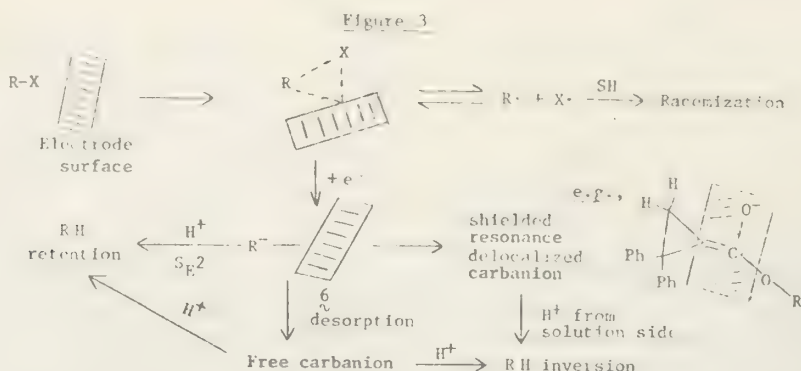
The potential dependence of the reduction of cyclohexane-1,4-dione to cis- and trans-1,4-cyclohexanediol (cis-trans isomer ratio = 8:1 at -1.9V vs. saturated calomel electrode on Hg) and the fact that the cathodic reduction of 4-hydroxycyclohexanone gives a cis-trans ratio of 1, suggest that adsorption plays a role in defining the stereochemistry of the reaction.²²

Further evidence for adsorbed ketyl radicals has come from recent electrocapillary studies of adsorption, potentiostatic current-voltage curves and adsorption isotherms for acetophenone²³ and steady and non-steady state potentiostatic studies of the reduction of acetone.²⁴

Reduction of Alkyl Halides. The reduction of alkyl halides is stepwise, proceeding through the radical, and then the carbanion which is subsequently protonated.²⁵ The original postulates concerning the stereochemical course of these reductions were made by Elving et al. who suggested that cleavage of carbon-halogen bonds was analogous to nucleophilic substitution with the cathode acting as a nucleophile.^{26a,b} B. Czochralska postulated a similar mechanism to account for the observed 77-92% inversion of configuration in the reduction of (-)-2-phenyl-2-chloropropionic acid at a mercury cathode.²⁷ It was suggested that the electrode attacked at carbon in an S_N2 process causing inversion of configuration with subsequent rapid protonation with retention of configuration. This mechanism is no longer accepted. Rather, it is thought that inversion occurs through protonation of an electrode shielded carbanion. Annino et al. have suggested that when the group adjacent to the C-X bond is carboxyl or carbomethoxy, the carbanion is formed through electrode attack on the C-X bond with retention of configuration, but that the carbanion rapidly becomes planar through resonance stabilization. The electrode then shields one side of the flat carbanion causing protonation to occur on the solution side. The result is overall inversion of configuration.^{28a,b,c}

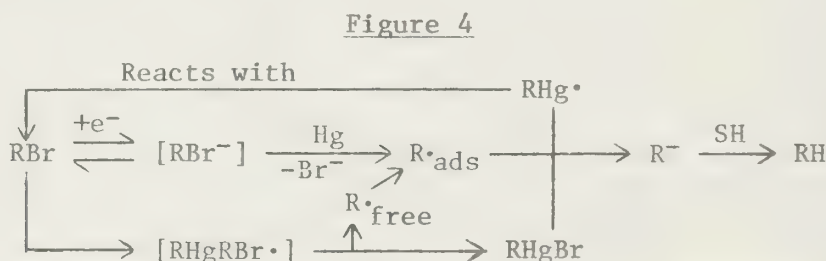
Several studies of the electrochemical reduction of cyclopropyl halides^{28a,b;29a,b} have shown that the reduction generally proceeds with overall (partial) retention of configuration. The initial report of Walborsky et al. suggested that adsorbed radicals and organomercurial intermediates produced 63% retention of configuration in the reduction of optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane.³⁰ The stereochemistry of cyclopropyl halide reductions is affected by the supporting electrolyte, solvent, electrode material, the halogen and substituents at the reaction site.^{29b} This suggests that the reduction involves adsorbed intermediates. R. Annino et al., in two studies of the electrochemical reduction of optically active bromocyclopropanes and geminal dihalocyclopropanes,^{28a,b} have suggested that the stereochemistry (which varies from 56% inversion to 38% retention of configuration) of the electrochemical reduction of alkyl halides

is roughly paralleled by zinc or lithium amalgam reductions and involves a complex reaction mechanism involving several types of adsorbed intermediates. (See Figure 3.)



The initial attack by the electrode is on the halogen or perpendicular to the halogen bond³¹ to give an electrode complex with the same overall configuration as the reactant. The overall stereochemistry is controlled by a stereoselective reaction of the electrode shielded carbanion (δ) with the solvent or a proton.

More recently, Walborsky *et al.*^{29b} have isolated organomercury compounds from the electrolysis of 1-halo-1-methyl-2,2-diphenylcyclopropanes and have presented current-time curves which suggest the involvement of organomercurial intermediates in the electrochemical reduction of alkyl halides. They have postulated a complex mechanism of adsorption control of stereochemistry summarized in Figure 4.



The free radicals involved in the organomercurial pathways are thought to account for the loss of stereospecificity. On glassy carbon cathodes where the organomercurial pathways are inoperative, the stereospecificity increases. Reduction of (+)-(S)-1-bromo-1-methyl-2,2-diphenylcyclopropane at mercury yields (-)-(R)-1-methyl-2,2-diphenylcyclopropane with overall retention of configuration, the optical purity being 25%, while in the same solution on a glassy carbon cathode, the optical purity is 47%. The loss of stereospecificity on addition of iodide ion (specifically adsorbed at cathodic potentials) during the reduction of cyclopropyl bromides may suggest surface phenomena involving adsorbed intermediates.

In all alkyl halide reductions involving carbanions, it is difficult to separate adsorption effects from solvation effects on the stereochemistry.³²

Asymmetric Reductions. Evidence that adsorption plays an important role in determining the stereochemistry of electrochemical reactions has come from the study of asymmetric reductions. The first indication that asymmetric electrochemical reductions were possible was the report by Murray and Kodama that enantiomeric copper(II) tartrates and cadmium (II) alanates exhibit different electrochemical properties in the presence of adsorbed optically

active brucine.³³ In 1967, Courley, Grimshaw and Millar³⁴ found that addition of strongly adsorbed alkaloids with asymmetric centers (Yohimbine, Narcotine, Sparteine) in the reduction of 4-methylcoumarin yielded 3,4-dihydro-4-methylcoumarin with up to 19% optical purity. The ratio of alkaloid to 4-methylcoumarin was approximately 0.07, and it was determined that the base was not destroyed in the reduction. Further work on the 4-methylcoumarin system has indicated that the stereochemistry may be controlled by the steric bulk of the alkyl groups attached to the protonated nitrogen of the adsorbed alkaloid.³⁵

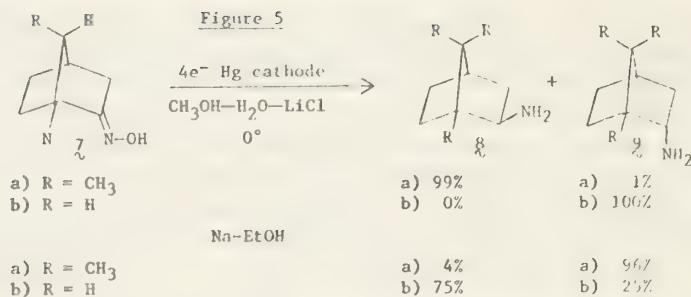
A series of experiments by Horner *et al.* on the asymmetric reduction of acetophenone to phenylmethylcarbinol,³⁶ acetophenone-N-benzylimine to N-benzyl- α -phenylethylamine,³⁷ and alkylaryl ketones to the corresponding carbinols^{38a,b} in the presence of optically active electrolytes such as (-)- and (+)-ephedrine hydrochloride have provided strong evidence that the chiral electrolytes present in the double layer influence the adsorption of the substrates and thereby affect the stereochemistry of the reduction product. The optical purities were all less than 10% and were found to depend on the chiral electrolyte used, the temperature (lower temperatures gave higher optical purity), the concentration of the chiral electrolyte and the structure of the substrate. The absolute configuration of the reduction product was found to have a complex dependence on the absolute configuration and structure of the chiral electrolyte. Kariv *et al.*, in a study of the asymmetric reduction of acetophenone in the presence of optically active alkaloids also concluded that the asymmetry is induced through a specific interaction of acetophenone with the adsorbed alkaloid.³⁹ It was postulated that the reason quinine and quinidine produced higher optical yields of carbinol than cinchonine and cinchonidine was that they were more strongly adsorbed on the electrode surface. The two most recent studies of the asymmetric reduction of acetophenone^{40a,b} have confirmed the surface nature of the reaction. The electrode material, the current density and the electrode potential were all found to influence the optical purity of the product.

Two recent studies on the reduction of phenylglyoxalic acid to mandelic acid in the presence of adsorbed alkaloids have shown that the extent of the asymmetric induction (optical purity of mandelic acid = 20% maximum) depends on complex interactions between the adsorbed alkaloids, the electrode surface, and adsorbed phenylglyoxalic acid.^{41a,b}

Recently, the reductions of 2- and 4-acetylpyridine to the corresponding carbinol in high chemical yields (80%) and optical yields of close to 50% have been accomplished using the strongly adsorbed alkaloid strychnine.^{41a,b}

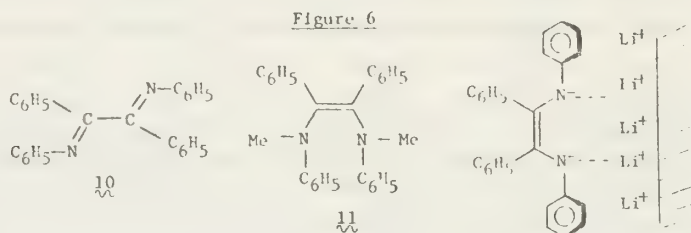
The heterogeneous surface nature of electrochemical reductions has been emphasized by the recent development of chiral electrodes where the surface has been modified by covalently bonding chiral amino acid esters to acidic surface sites. Electrodes of the (R) or (S) configuration can be made and induce opposite chirality in the reduction products of 4-acetylpyridine.^{43a,b}

Miscellaneous Reductions. The product amines (8 and 9) of the electrochemical reduction of camphor oxime (7a) and norcamphor oxime (7b) are of opposite stereochemistry to those formed in sodium-alcohol reductions (Figure 5).⁴⁴



The reduction may involve attack of the electrode on the least hindered side of the oxime followed by protonation on the electrode face.

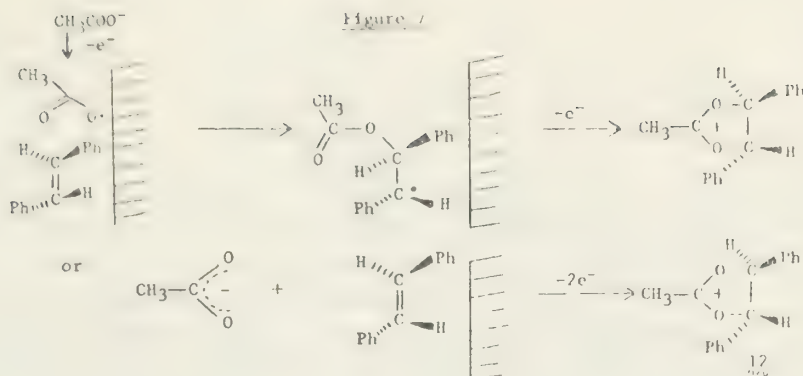
The reduction of the diimine 10 in the presence of LiCl and chloromethane has recently been suggested to proceed through an adsorbed dianionic species (Figure 6) on the basis of the predominance of the cis dimethylated product 11.



II. Oxidations.

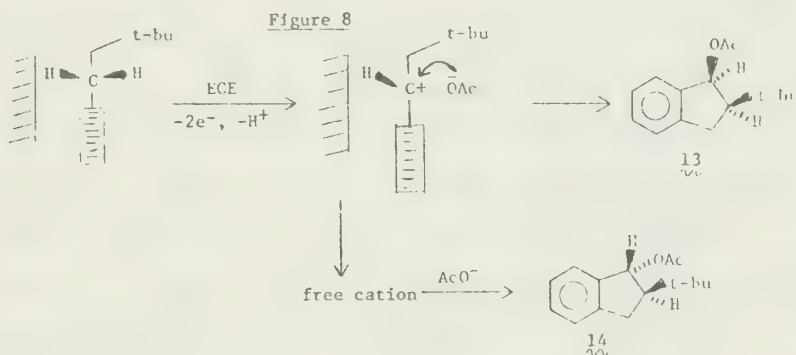
Addition of Radicals to Dienes. Free radicals produced in Kolbe electrolyses are capable of attacking 1,3-dienes present.⁴⁵ Stereoselectivity has been observed in the addition of methyl radicals to 1,3-dienes.^{46a,b} The electrolysis of potassium acetate in a methanolic solution of butadiene yields only the cis-3-methyl-3-hexene. Similarly, ethyl radicals produced from the electrolysis of potassium propionate react with butadiene to give only trans-4-octene. These results have been interpreted in terms of adsorption of the butadiene and isoprene on the platinum electrode in their most stable conformations (s-trans for butadiene and s-cis for isoprene) before reaction with the electrochemically generated radicals. Though the work has been widely cited, there are a number of difficulties involved in the experiments and the assumption of adsorption control.

Acetoxylation and Methoxylation. T. Inoue et al.⁴⁷ found that the electrolysis of sodium methoxide in methanol in the presence of cis- and trans-stilbenes gave a mixture of meso- and dl-hydrobenzoin dimethyl ethers. More cis-adduct than trans-adduct was formed in each case. This was taken to indicate addition of a methoxyl radical followed by electrochemical oxidation and attack by methoxide on the same side of an adsorbed intermediate. Other explanations are possible.^{48a,b} Later, Mango and Bonner⁴⁹ found that the electrolysis of sodium acetate in the presence of trans-stilbene under anhydrous conditions produced mainly meso-hydrobenzoin diacetate. Under moist conditions, threo-2-acetoxy-1,2-diphenyl ethanol was the main product. None of the erythro-hydroxyacetate was obtained. They concluded that a cyclic acetoxonium intermediate (12) was formed stereoselectively on the anode. Possible mechanisms are shown in Figure 7.



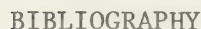
The inversion of configuration during the anodic addition of benzoyloxy groups to *cis*-stilbene suggests that adsorption may not control the stereochemistry in these oxidations.^{48a}

The anodic acetoxylation of 2-*t*-butylindane on Pt in HOAc/0.5 M NaOAc produces a *cis-trans* ratio of the product side chain acetate (1-acetoxy-2-*t*-butylindane) equal to 16:84. This is in contrast to the 2:98 *cis-trans* ratio obtained in the homogeneous solvolysis of the 1-(nitrobenzoyloxy)-2-*t*-butylindane in HOAc/0.5 M NaOAc at 75° C.⁵⁰ It was suggested that the 2-*t*-butylindane is adsorbed on the surface of the electrode with the *t*-butyl group away from the electrode surface. (See Figure 8).



In this adsorbed orientation, anodic substitution yields the less stable *cis* isomer 13 while attack on the free cation leads to the *trans* isomer 14. On Pt, where the substrate is more strongly adsorbed, the *cis-trans* ratio is a factor of three higher than on the weaker adsorbing carbon or lead oxide electrodes. Similar results have been observed in the anodic acetoxylation of 1-*t*-butylacenaphthene.⁵¹

Miscellaneous Oxidations. The stereoselectivity of the anodic phenolic coupling of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (15) has been found to be due to adsorption of intermediate radical species.⁵² Three separable enantiomeric pairs (Figure 9) are possible. Only the *SS*-rotamer A and *RR*-rotamer A are produced in the anodic electrolysis of racemic (15) on graphite. If the reacting molecules are adsorbed on the surface with the methyl groups away from the surface, only those with identical configurations can approach closely enough to couple without severe methyl methyl interaction. The rotamer A is formed as a consequence of the aromatic rings being adsorbed parallel to the electrode surface while the heterocyclic rings are bent away from the surface.



1. D. C. Grahme, Chem. Rev., 41, 441 (1947).
2. (a) J. O'M Bockris and A. K. N. Reddy, "Modern Electrochemistry," New York, Plenum Press, 1970, vol. 2, p. 623ff; (b) A. J. Fry, "Synthetic Organic Electrochemistry," New York, Harper and Row, 1972, p. 48ff.
3. (a) D. M. Mohilner, in A. J. Bard, ed., "Electroanalytical Chemistry," New York, Marcell Dekker, 1966, vol. 1, p. 241ff; (b) R. Payne, Advances Electrochem. Eng., 7, 1 (1970).
4. (a) A. J. Fry, Footschritte der Chemischen Forschung, 34, 1 (1972); (b) L. Ebersson and L. Horner, in M. Baizer, ed., "Organic Electrochemistry," New York, Marcell Dekker, 1973, p. 869ff.
5. K. N. Campbell and E. E. Young, J. Am. Chem. Soc., 65, 965 (1943).
6. (a) H. Lindlar, Helv. Chim. Acta, 35, 446 (1952); (b) H. Lindlar and R. Dubois, Org. Syn., 46, 89 (1966).
7. J. B. Lee and P. Cashmore, Chem. Ind., 1758 (1966).
8. A. P. Tomilov, S. G. Mairanovskii, M. Ya. Fioshin, and V. A. Smirnov, "Electrochemistry of Organic Compounds," New York, Halsted Press, 1972, p. 138.
9. S. Wawzonek and D. Wearing, J. Am. Chem. Soc., 81, 2067 (1959).
10. L. Horner and H. Roder, Liebigs Ann. Chem., 723, 11 (1969).
11. D. Seebach and H. A. Oei, Angew. Chem. Int. Ed. Eng., 14(9), 634 (1975).
12. (a) M. J. Allen, J. Org. Chem., 15, 435 (1949); (b) M. J. Allen, J. Chem. Soc., 1598 (1951); (c) M. J. Allen, J. E. Fearn, and H. A. Levine, J. Chem. Soc., 2270 (1952).
13. (a) J. H. Stocker and R. M. Jenevein, J. Org. Chem., 33, 294 (1968); (b) J. H. Stocker and R. M. Jenevein, *ibid.*, 34, 2807, 2810 (1969); (c) J. H. Stocker and R. M. Jenevein, Collect. Czech. Chem. Commun., 36(2), 925 (1971); (d) R. J. Holman and J. H. P. Utley, Tetrahedron Lett., 1553 (1974).
14. E. J. Rudd and B. E. Conway, Trans. Faraday Soc., 67, 440 (1971).
15. V. J. Puglisi, G. L. Clapper, and D. H. Evans, Anal. Chem., 41(2), 279 (1969).
16. T. Nonaka, A. Udagawa, and K. Odo, Chem. Lett., 1261 (1975).
17. E. Touboul and G. Dana, Tetrahedron, 31, 1925 (1975).
18. P. Anziani, A. Anbry, and R. Cornubert, Compt. Rend., 225, 878 (1947).
19. L. Mandell, R. M. Powers, and R. A. Day, J. Am. Chem. Soc., 80, 5284 (1958).
20. T. Shono and M. Mitani, Tetrahedron, 28, 4747 (1972).

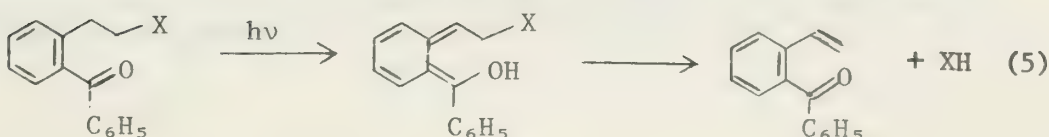
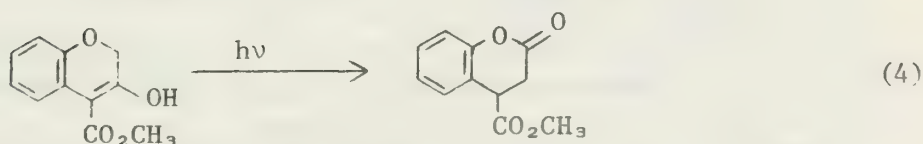
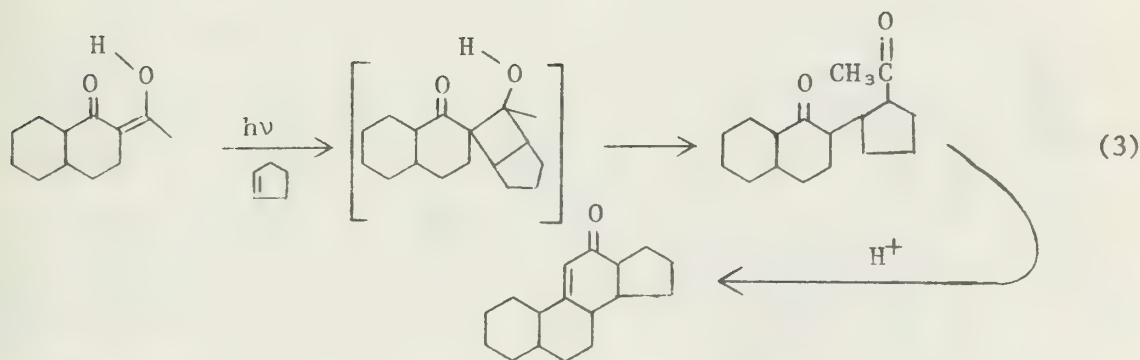
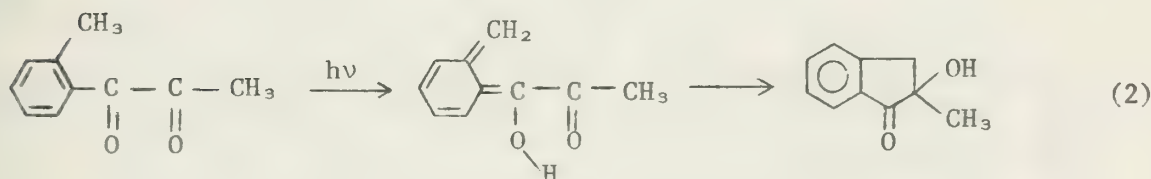
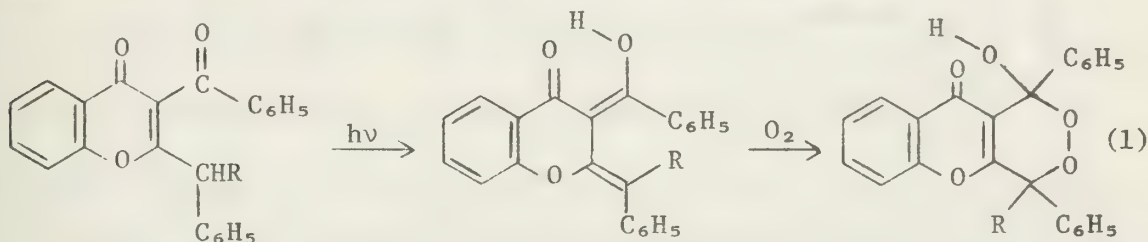
21. (a) J. P. Coleman, R. J. Kobylecki, and J. H. P. Utley, *Chem. Commun.*, 104 (1971); (b) J. P. Coleman, R. J. Holman, and J. H. P. Utley, *J. Chem. Soc. Perkin II*, 879 (1976).
22. E. Kariv and B. J. Cohen, *J. C. S. Perkin II*, 509 (1972).
23. B. E. Conway, E. J. Judd, and L. G. M. Gordon, *Discuss. Faraday Soc.*, 45, 87 (1968).
24. O. R. Brown and K. Lister, *Discuss. Faraday Soc.*, 45, 106 (1968).
25. M. Von Stackelberg and W. Stracke, *Z. Elektrochem.*, 53, 118, (1949).
26. (a) P. J. Elving, *Rec. Chem. Progr.*, 14, 99 (1953); (b) P. J. Elving and B. Pullman, *Advan. Chem. Phys.*, 3, 1 (1961).
27. B. Czochralska, *Chem. Phys. Lett.*, 1, 239 (1967).
28. (a) R. Annino, R. E. Erickson, J. Michalovic, and B. McKay, *J. Am. Chem. Soc.*, 88(19), 4424 (1966); (b) R. E. Erickson, R. Annino, M. D. Scanlon, and G. Zon, *ibid.*, 91(17), 1767 (1969); (c) K. Butin, *Russ. Chem. Revs.*, 40(6), 525 (1971).
29. (a) A. J. Fry and R. H. Moore, *J. Org. Chem.*, 33, 1283 (1968); (b) J. L. Webb, C. K. Mann, and H. M. Walborsky, *J. Am. Chem. Soc.*, 92, 2042 (1970).
30. C. K. Mann, J. L. Webb, and H. M. Walborsky, *Tetrahedron Lett.*, 2249 (1966).
31. F. L. Lambert, *J. Org. Chem.*, 31, 4184 (1966).
32. E. L. Eliel, "The Stereochemistry of Carbon Compounds," New York, McGraw-Hill, 1962, p. 384ff.
33. R. W. Murray and M. Kodama, *Anal. Chem.*, 37, 1759 (1965).
34. R. N. Gourley, J. Grimshaw, and P. G. Millar, *Chem. Commun.*, 1278 (1967).
35. R. N. Gourley, J. Grimshaw, and P. G. Millar, *J. Chem. Soc. (C)*, 2318 (1970).
36. L. Horner and D. Degner, *Tetrahedron Lett.*, 56, 5889 (1968).
37. L. Horner and D. Degner, *Tetrahedron Lett.*, 42, 3679 (1970).
38. (a) L. Horner and D. Degner, *Tetrahedron Lett.*, 17, 1245 (1971); (b) L. Horner, D. Degner, and D. Skaletz, *Chem. Ing. Techn.*, 44(4), 209 (1972).
39. E. Kariv, H. A. Terni, and E. Gileadi, *J. Electrochem. Soc.*, 120, 639 (1973).
40. (a) E. Kariv, H. A. Terni, and E. Gileadi, *Electrochim. Acta*, 18, 433 (1973); (b) L. Horner and R. Schneider, *Tetrahedron Lett.*, 33, 3133 (1973).
41. (a) M. Jubault, E. Raoult, and D. Peltier, *C. R. Acad. Sc. Paris*, 277, 583 (1973); (b) M. Jubault, E. Raoult, and D. Peltier, *Electrochim. Acta*, 19, 865 (1974).
42. (a) J. Kopilov, S. Shatzmiller, and E. Kariv, *Electrochim. Acta*, 21, 535 (1976); (b) J. Hermolin, J. Kopilov, and E. Gileadi, *J. Electroanal. Chem.*, 71, 245 (1976).
43. (a) B. F. Watkins, J. R. Behling, E. Kariv, and L. Miller, *J. Am. Chem. Soc.*, 97(12), 3549 (1975); (b) B. E. Firth, L. L. Miller, M. Mitani, T. Rogers, J. Lennox, and R. W. Murray, *ibid.*, 98, 8271, 8272 (1976).
44. A. J. Fry and J. H. Newberg, *J. Am. Chem. Soc.*, 89(24), 6374 (1967).
45. R. V. Lindsey, Jr. and M. L. Peterson, *J. Am. Chem. Soc.*, 78, 2073 (1956).
46. (a) W. B. Smith and H.-G. Gilde, *J. Am. Chem. Soc.*, 81, 5325 (1959); (b) W. B. Smith and H.-G. Gilde, *J. Am. Chem. Soc.*, 83, 1355 (1961).
47. T. Inoue, K. Koyama, T. Matsuoka, K. Matsuoka, and S. Tsutsumi, *Tetrahedron Lett.*, 1409 (1963).
48. (a) K. Koyama, T. Ebara, T. Tani, and S. Tsutsumi, *Can. J. Chem.*, 47, 2484 (1969); (b) T. Inoue, K. Koyama, T. Matsuoka, and S. Tsutsumi, *Bull. Chem. Soc. Japan*, 40, 162 (1976).
49. F. D. Mango and W. A. Bonner, *J. Org. Chem.*, 29, 1367 (1964).
50. L. Ebersson and H. Sternerup, *Acta Chem. Scand.*, 26, 1431 (1972).
51. J. P. Dirlam and L. Ebersson, *Acta Chem. Scand.*, 26, 1452 (1972).
52. J. M. Bobbitt, I. Noguci, H. Yagi, and K. H. Weisgraber, *J. Am. Chem. Soc.*, 93, 3551 (1971).

Reported by Reginald A. Booker

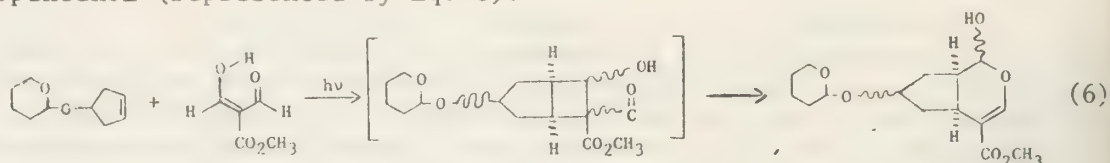
February 3, 1977

Benzophenone is readily reduced photochemically in the presence of hydrogen donors to give benzopinacol via a ketyl radical intermediate.²⁵ In 1961, N. C. Yang² noticed that photochemical pinacol reduction is suppressed if the benzophenone is substituted at the ortho position by an alkyl group containing an α -hydrogen. Instead, o-alkylbenzophenone undergoes intramolecular hydrogen transfer to give the corresponding enol under the influence of ultraviolet light. Yang²⁻⁴ and other workers⁵⁻⁸ have shown through physical and chemical evidence that the enolization process is an intramolecular photochemical reaction analogous to the Norrish type II process. Since that time, extensive work has been directed toward determining the scope and limitations of enol photochemistry.²⁻²²

Recently, a number of reports have appeared in the literature directing attention to the synthetic utility of enol photochemistry. Synthetically, enol photochemistry has been useful in cyclization reactions (represented by Eqs. 1, 2, and 3),^{8,15,22} ring opening and ring closure reactions (represented by Eq. 4),²¹ and elimination reactions (represented by Eq. 5).¹⁸



Through enol photochemistry, the tetrahydrocoumalate unit typical of iridoids was prepared in a single operation by the photochemical cycloaddition of 2-formylmalonaldehydic acid methyl ester to the tetrahydropyranyl ether of 3-cyclopentenol (represented by Eq. 6).²⁰



BIBLIOGRAPHY

1. A. Padwa and A. Au, *J. Am. Chem. Soc.*, **98**, 5581 (1976).
2. N. C. Yang and C. Rivas, *J. Am. Chem. Soc.*, **83**, 2213 (1961).
3. N. C. Yang and M. J. Jorgenson, *Tetrahedron Lett.*, 1203 (1964).
4. E. F. Zwicker, L. I. Grossweiner, and N. C. Yang, *J. Am. Chem. Soc.*, **85**, 2671 (1963).
5. J. N. Pitts, Jr., H. W. Johnson, Jr., and T. Kuwana, *J. Phys. Chem.*, **66**, 2456 (1962).
6. E. F. Ullman and K. R. Huffman, *Tetrahedron Lett.*, 1863 (1965).
7. K. R. Huffman, M. Loy, and E. F. Ullman, *J. Am. Chem. Soc.*, **87**, 5417 (1965).
8. W. A. Henderson, Jr. and E. F. Ullman, *J. Am. Chem. Soc.*, **87**, 5424 (1965).
9. Y. Tamura, S. Fukumori, S. Kato, and Y. Kita, *J. Chem. Soc., Chem. Commun.*, 285 (1974).
10. N. D. Heindel, E. W. Sarver, and M. A. Pfau, *Tetrahedron Lett.*, 3579 (1968).
11. M. A. Pfau, N. D. Heindel, and T. F. Lemke, *C. R. Acad. Sci.*, **261**, 1017 (1965).
12. (a) R. Bishop and N. K. Hamer, *Chem. Commun.*, 804 (1969); (b) R. Bishop and N. K. Hamer, *J. Chem. Soc. C*, 1193 (1970); (c) N. K. Hamer and C. J. Samuel, *J. Chem. Soc., Chem. Commun.*, 470 (1972); (d) N. K. Hamer and C. J. Samuel, *J. Chem. Soc. Perkin Trans. 2*, 1316 (1973).
13. T. L. Burkoth and E. F. Ullman, *Tetrahedron Lett.*, 145 (1970).
14. K. Maruyama, K. Ono, and J. Osugi, *Bull. Chem. Soc. Jpn.*, **45**, 847 (1972).
15. K. Ogata and K. Takagi, *J. Org. Chem.*, **39**, 1385 (1974).
16. (a) G. Porter and M. F. Tchir, *Chem. Commun.*, 1372 (1970); (b) G. Porter and M. F. Tchir, *J. Chem. Soc. A*, 3772 (1971).
17. N. D. Heindel, J. Molnar, and M. Pfau, *Chem. Commun.*, 1372 (1970).
18. S. S. Tseng and E. F. Ullman, *J. Am. Chem. Soc.*, **98**, 541 (1976).
19. P. S. Wagner and C. P. Chen, *J. Am. Chem. Soc.*, **98**, 241 (1976).
20. (a) G. Buchi, J. A. Carlson, J. F. Powell, Jr., and L. F. Tietze, *J. Am. Chem. Soc.*, **92**, 2165 (1970); (b) G. Buchi, J. A. Carlson, J. F. Powell, Jr., and L. F. Tietze, *ibid.*, **95**, 540 (1973).
21. (a) A. Padwa and A. Au, *J. Am. Chem. Soc.*, **97**, 242 (1975); (b) A. Padwa and G. A. Lee, *ibid.*, **95**, 6147 (1973); (c) A. Padwa and G. A. Lee, *ibid.*, **96**, 1634 (1974); (d) A. Padwa, D. Dehm, T. Oine, and G. A. Lee, *ibid.*, **97**, 1837 (1975); (e) A. Padwa, A. Au, G. A. Lee, and W. Owens, *ibid.*, **98**, 3555 (1976).
22. H. Nazaki, M. Kurita, T. Mori, and R. Noyori, *Tetrahedron*, **24**, 1821 (1968).
23. C. H. Depuy and O. L. Chapman, "Molecular Reactions and Photochemistry," K. L. Rinehart, Jr., Ed., Prentice Hall, Englewood Cliffs, New Jersey, 1972.
24. N. J. Turro, "Molecular Photochemistry," R. Breslow and M. Karplus, Ed., W. A. Benjamin, Amsterdam, N. Y., 1965.
25. C. S. Hammond and W. M. Moore, *J. Am. Chem. Soc.*, **81**, 6334 (1959).

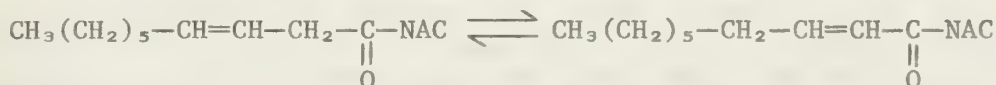
THE CHEMISTRY OF ENZYME SUICIDE INHIBITORS

Reported by Craig Kubitschek

February 10, 1977

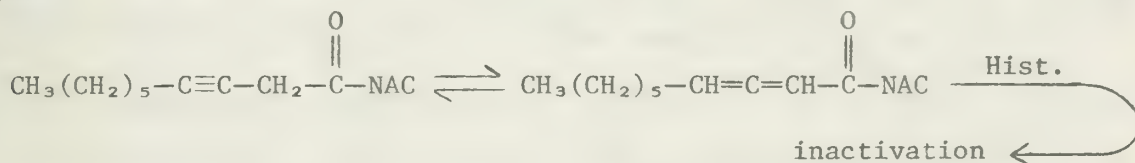
Suicide inactivators of enzymes are substrates which can bind to active sites and then be converted by the catalytic action of the enzyme into chemically reactive species that irreversibly modify the protein.^{1,2} The enzyme, which becomes permanently deactivated, has thus committed "suicide" by the process of carrying out its catalytic function. An important use of such inhibitors is in the elucidation of the structures of enzyme binding sites. Moreover, these inhibitors may prove to be of considerable pharmacological importance. The action of the inhibitor requires both binding and catalysis by the enzyme; consequently, extremely specific inhibitors may be devised. Indeed, a number of antibiotics are believed to act by this type of mechanism.^{3,4} This seminar will discuss the mechanisms of several cases of suicide inhibition as well as general approaches to the design of such compounds.

The paradigm of this type of inhibitor was reported by Bloch and co-workers in their studies on β -hydroxydecanoyl thioester dehydrase,⁵⁻⁷ a key enzyme in the synthesis of fatty acids. This enzyme catalyzes the isomerization of β,γ -unsaturated thioesters, among other reactions.



NAC = N-acetylsteamine, $-\text{S}(\text{CH}_2)_2-\text{NH}-\text{CO}-\text{CH}_3$

The enzyme is irreversibly inactivated by the substrate analogue 3-decynoyl-NAC, which is made active by isomerization to the corresponding conjugated allene; the allene reacts with an active site histidine, thus disabling the enzyme.



A similar inhibition of a steroid isomerase has recently been reported.⁸

In general, three requirements must be met for suicide inactivation to occur. First, the enzyme must be able to convert the unreactive species into a reactive one. Second, the reactive species must come within bonding distance of an appropriate amino acid residue while it is still at or near the active site. Finally, the reactive species must remain at the active site for a sufficient length of time for bond formation to occur.⁹ Enzymes that utilize covalent catalysis, such as the pyridoxal-containing enzymes, satisfy these requirements very well. The pyridoxal-cofactored enzymes form Schiff's bases with their amine substrates; these Schiff's bases can be converted into highly reactive inhibitors, usually Michael acceptors, by enzymatic dehydration,¹⁰ dehydrohalogenation^{11,12} or related pathways,¹³ or by rearrangement of double¹⁴⁻¹⁷ or triple^{18,19} bonds via proton abstraction.

Numerous examples of suicide inhibition of flavin-linked enzymes have been reported as well. The most common mechanisms of inactivation involve oxidation of an unsaturated hydroxy acid²⁰⁻²³ or amine.²⁴⁻²⁶ In addition, a recent report describes the synthesis of an inhibitor that functions via an allyl bromide intermediate.⁹

While covalent catalysis plays an important role in the above reactions, it is apparently not essential in all cases. Plasma amine oxidase has been inhibited by 1-amino-2-alkynes,^{27,28} presumably through a Schiff's base intermediate in a manner analogous to the mechanism of the pyridoxal-linked enzymes. However, this enzyme can also be inhibited by glycine esters; the presumed active intermediate in this process is a ketene.²⁹

Suicide inhibitors have already proved valuable in elucidating the pathways of biological reactions. The design and synthesis of these inhibitors should prove to be a productive field of study for organic chemists.

BIBLIOGRAPHY

1. R. R. Rando, *Science*, 185, 320 (1974).
2. R. H. Abeles and A. L. Maycock, *Acc. Chem. Res.*, 9, 313 (1976).
3. R. R. Rando, *Biochem. Pharm.*, 24, 1153 (1975).
4. R. R. Rando, *Acc. Chem. Res.*, 8, 281 (1975).
5. G. M. Helmkamp, Jr., R. R. Rando, D. J. H. Brock, and K. Bloch, *J. Biol. Chem.*, 243, 3229 (1968).
6. K. Endo, G. M. Helmkamp, Jr. and K. Bloch, *J. Biol. Chem.*, 245, 4293 (1970).
7. M. Morisaki and K. Bloch, *Biochemistry*, 11, 309 (1972).
8. F. H. Batzold and C. H. Robinson, *J. Am. Chem. Soc.*, 97, 2576 (1975).
9. R. R. Rando, *J. Am. Chem. Soc.*, 97, 4438 (1975).
10. A. T. Phillips, *Biochim. Biophys. Acta*, 151, 523 (1968).
11. Y. Morino and M. Okamoto, *Biochem. Biophys. Res. Comm.*, 50, 1061 (1973).
12. R. B. Silverman and R. H. Abeles, *Biochemistry*, 15, 4718 (1976).
13. L. J. Fowler and R. A. John, *Biochem. J.*, 130, 569 (1972).
14. R. R. Rando, *J. Am. Chem. Soc.*, 98, 6762 (1976).
15. R. R. Rando, *Biochemistry*, 13, 3859 (1974).
16. R. R. Rando, *Nature*, 250, 586 (1974).
17. J. Giovanelli, L. D. Owens, and S. H. Mudd, *Biochim. Biophys. Acta*, 227, 671 (1971).
18. M. J. Jung and B. W. Metcalf, *Biochem. Biophys. Res. Commun.*, 67, 301 (1975).
19. R. H. Abeles and C. T. Walsh, *J. Am. Chem. Soc.*, 95, 6124 (1973).
20. T. Cromartie, J. Fisher, G. Kacorowski, R. Laura, P. Marcotte, and C. Walsh, *J.C.S. Chem. Commun.*, 597 (1974).
21. C. T. Walsh, A. Schonbrunn, O. Lockridge, V. Massey, and R. H. Abeles, *J. Biol. Chem.*, 247, 6004 (1972).
22. C. T. Walsh and R. Kaback, *J. Biol. Chem.*, 248, 5456 (1973).
23. C. T. Walsh, R. H. Abeles, and H. R. Kaback, *J. Biol. Chem.*, 247, 7858 (1972).
24. H. Y. K. Chuang, D. R. Patek, and Leslie Hellerman, *J. Biol. Chem.*, 249, 2381 (1974).
25. C. T. Walsh, *J. Am. Chem. Soc.*, 97, 2270 (1975).
26. A. L. Maycock, R. H. Abeles, and T. P. Singer, *Biochemistry*, 15, 114 (1976).
27. R. C. Hevey, J. Babson, A. L. Maycock, and R. H. Abeles, *J. Am. Chem. Soc.*, 95, 6125 (1973).
28. R. R. Rando and J. de Mairena, *Biochem. Pharm.*, 23, 463 (1973).
29. A. L. Maycock, R. H. Suva, and R. H. Abeles, *J. Am. Chem. Soc.*, 97, 5613 (1975).

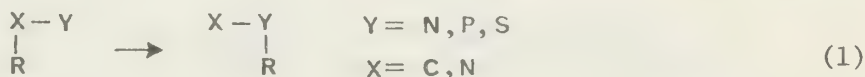
THE STEVENS REARRANGEMENT

Reported by Robert H. Foster ,

February 17, 1977

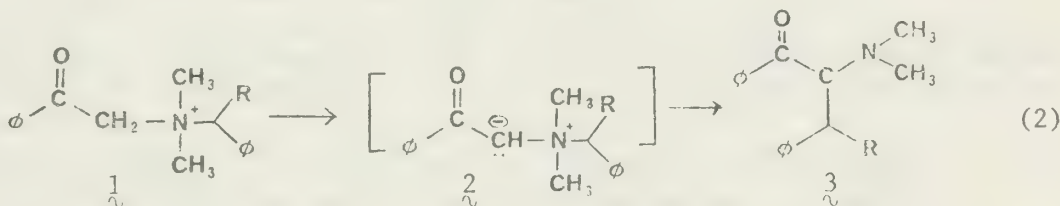
The Stevens rearrangement is a [1,2] alkyl migration to an atom with a lone pair of electrons. Its facility and yields are susceptible to the influences of substituent, solvent, temperature, and other variables. Changes in these parameters can result in high yields of side products arising from competing processes such as the Sommelet rearrangement, displacement, and Hoffman elimination. The recently discovered phenomena of CIDNP and Orbital Symmetry awareness have prompted a reexamination of the proposed mechanisms for the Stevens rearrangement. This abstract reports some recent research and developments therein.

Introduction. The Stevens rearrangement, discovered in 1928,¹ is the name given to a series of [1,2] sigmatropic rearrangements of ammonium, phosphonium, and sulphonium salts, as in Eq. 1. These are part of a larger



group of base catalyzed [1,2] migrations to an atom with a lone pair of electrons, such as the Meisenheimer (X = N, Y = O),³ Wittig (X = O, Y = C),⁴ and Wawzonek (X = N, Y = N)⁵ rearrangements,^{6,7} the last of which will be discussed as a Stevens rearrangement in this abstract.

The Stevens rearrangement is typified by the original system in which benzyldimethylphenacylammonium bromide (1) rearranges to α -dimethylamino- β -propiophenone (3) in base via the ylid 2 shown in Eq. 2 (R = H). Ylids



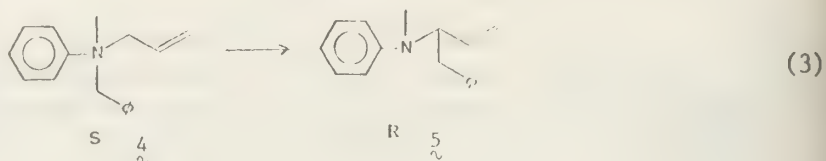
have been shown to be the rearrangement precursor by alternate syntheses, including the reaction of a tertiary amine with benzyne¹⁰ or a carbene.¹¹

Stevens substrates (i.e. 1) usually have no β -hydrogens⁹ and have at least one α -hydrogen whose abstraction is facilitated by a formally positively charged 'onium heteroatom and another group capable of ylid stabilization such as vinyl, phenyl, and benzoyl.⁹ Though few examples of simple alkyl migrations have been reported,^{14,15,16} secondary and tertiary alkyl migrating species do exist.^{17,18}

Background. A number of well substantiated mechanistic aspects of Stevens rearrangements led researchers to initial conclusions about reaction pathways. Stevens,¹⁹ and subsequently others²⁰ have shown in substituent studies and deuterium²¹ and C-14 labellings²² the inherent intramolecularity of the rearrangement by the demonstrable absence of cross-products.

A second observation was that of configuration in the migrating terminus. In an optically active Stevens substrate (1, R = $-\text{CH}_3$), α -phenyl-ethyl migration occurred with >90% retention of configuration.^{20,23}

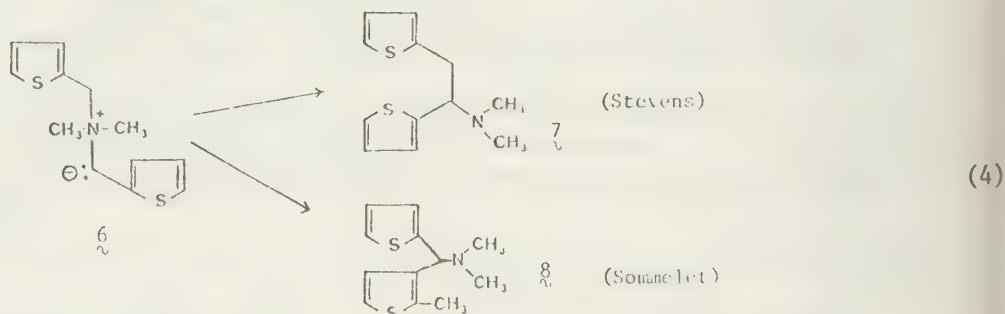
Interesting examples of stereoselection include transfer of ammonium chirality to carbon²⁴ (Eq. 3) and complete transfer of dissymmetry in bridged biphenyls.²⁵



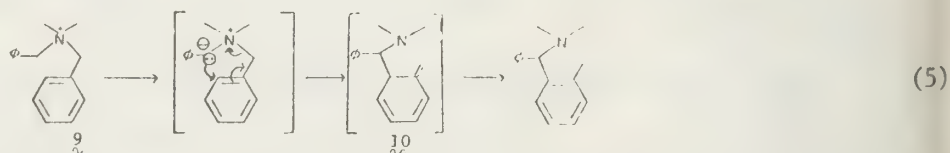
Most migrating groups are benzyl or α -substituted benzyis, though recent work has explored alternatives. The ideal migrating group had been thought of as one capable of stabilizing a negative charge;⁹ recent work (*vide infra*) indicates that the ability to stabilize a radical may also be important. Some of the less common migrating groups include 2-thenyl,²⁶ α - (but not β -) naphthyl,²⁷ neopentyl,¹⁵ adamantyl,¹⁴ 3-methyl-1-butynyl,¹⁸ and succinimidy1.²⁸

Competing Reactions. Three competing processes deserve mention---the Sommelet rearrangement, displacement reactions, and Hoffman elimination.

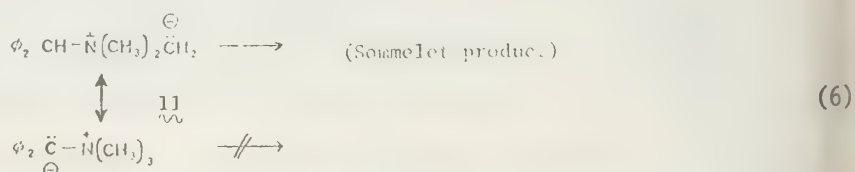
The Sommelet rearrangement²⁹ (Eq. 4) is perhaps the most major competitor of the Stevens rearrangement; they are thus often presented



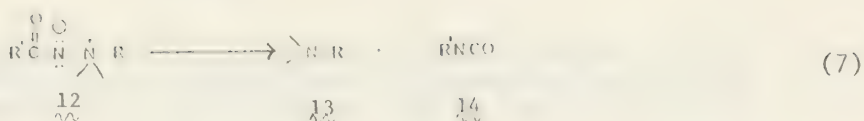
together.^{8,9} They may²⁶ or may not⁹ have a common ylid precursor. Like other [3,2] sigmatropic shifts,³⁰ the Sommelet rearrangement is a symmetry allowed³¹ concerted process considered to proceed via the pathway indicated



in Eq. 5. Ylid stability does not appear to govern the type of rearrangement undergone in all cases,³² as in the rearrangement of 11 (Eq. 6). Conditions which may favor one rearrangement over another are discussed elsewhere in this abstract.

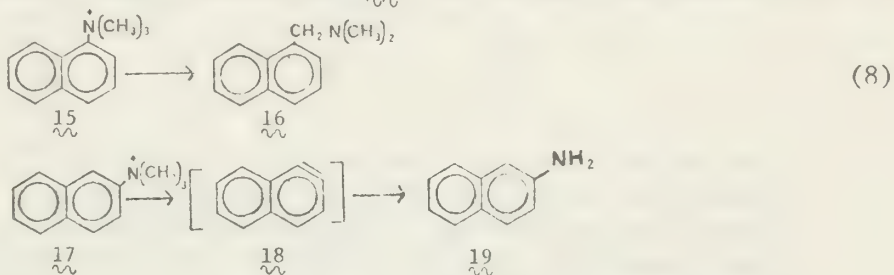


Displacement reactions are a second competing process. In one case,³³ displacement yielded the tertiary amine and the isocyanate (Eq. 7). Another



type of displacement yields the alkylated base and a tertiary amine. Thus, N,N,N-trimethyl-1-adamantylammonium hydroxide yielded, on vacuum pyrolysis, methanol and N,N-dimethyl-1-aminoadamantane³⁴ among the side products.

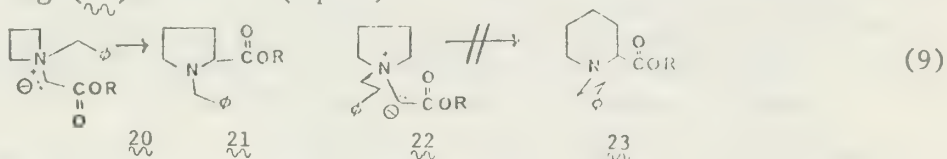
A third side reaction is Hoffman elimination.^{35,36} Most Stevens substrates have no β -protons; where they exist, Hoffman elimination can occur. In these cases, relative acidities may determine the reaction course. Consequently, β -naphthyltrimethylammonium (17) iodide gave naphthyne (Eq. 8)



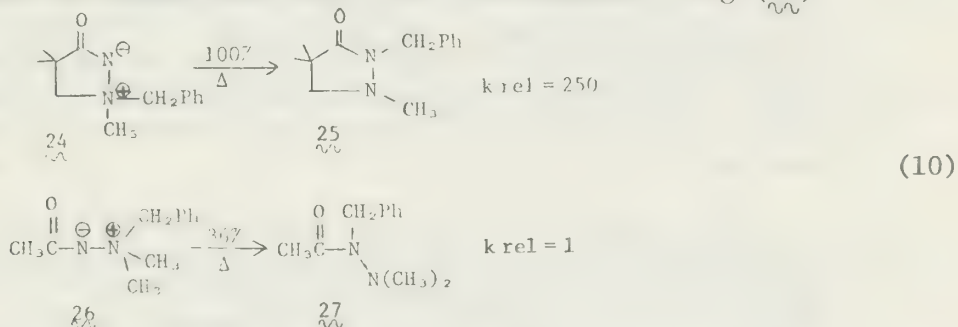
whereas the α -isomer (15) gave the Stevens product.²⁷ Alternatively,³⁷ Stevens rearrangements can occur in the presence of β -protons when Hoffman elimination is unfeasible. Hoffman elimination is also used in conjunction with the Stevens rearrangement to effect stereospecific³⁸ syntheses.³⁹

Reaction Variables. The factors and variables influencing the course of the reaction include relief of steric strain, the types of substituents on the ylid, the solvent, the base, and the temperature.

A driving force in some Stevens rearrangements appears to be relief of steric strain.^{11,17} Thus, in a reaction of cyclic ammonium salts, a four-membered ring (20) (requiring alkyl, not benzyl migration) rearranged whereas a five-membered ring (22) did not (Eq. 9).¹¹ The influence of strain relief



has also been observed in an aminimide rearrangement (Eq. 10),⁴⁰ where the sp^2 imide nitrogen is constrained in a 108° five-membered ring (24).

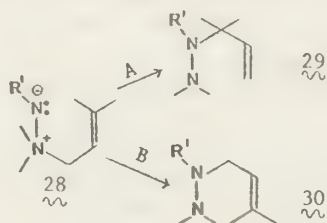


Rehybridization to an sp^3 geometry (109°) with simultaneous strain relief is advanced as the primary cause of the marked difference in reaction rates and yields.

Substituent effects have been studied for the benzyldimethylphenacylammonium bromides (1). Para-substituents on the migrating ring were found to accelerate the reaction in the order $\text{NO}_2 > \text{I}, \text{Br}, \text{Cl} > \text{CH}_3 > \text{H} > \text{OCH}_3$,^{41,42} and

on the phenacyl ring in the order $\text{OCH}_3 > \text{CH}_3 > \text{H} > \text{Halide} > \text{NO}_2$.⁴³ A Hammett plot⁸ for both sets of substituents resulted in a moderate linear fit--- ρ for the phenacyl ring = -0.38, and for the migratory benzyl, $\rho = +1.1$.

Ylid stability is thought to influence the course of the reaction.⁹ Stabilizing groups on the ylid include, in order of stabilizing ability:⁷ Benzoyl > Ethynyl > allyl > phenyl > alkyl. The influence of a stabilizing group can be seen in Eq. 11 where the hydrazinium salt (28, $\text{R}' = \text{alkyl}$)



(11)

rearranges via path A whereas the stabilized ylid (28, $\text{R}' = \text{benzoyl}$) rearranges via path B to form the Stevens product.⁴⁵ A number of stable ylids have been isolated as their monohydrates;⁴⁴ they readily undergo Stevens rearrangements, and the absence of customary carbonyl stretching frequency bands in the IR is taken as an indication of electron delocalization.

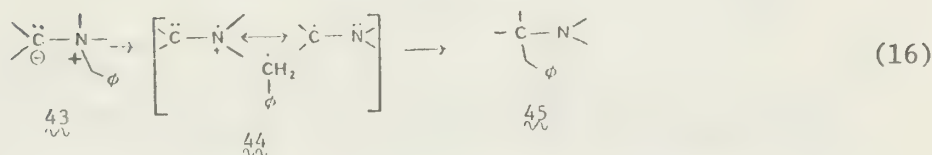
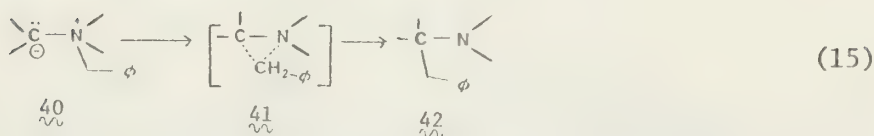
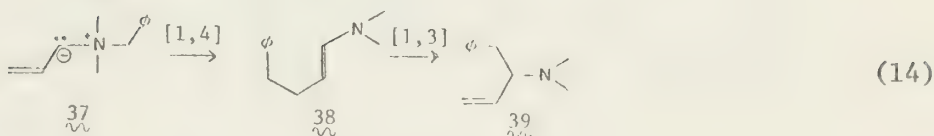
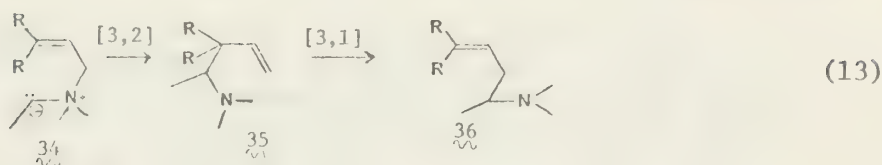
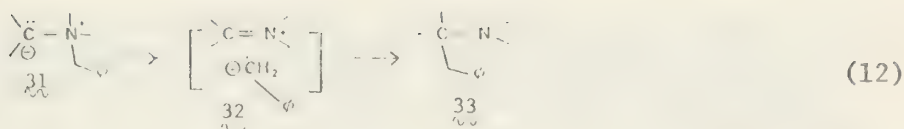
Since the solvation of ions seems to favor the competing processes,^{9,47} solvents for Stevens rearrangements tend to be non-polar, such as hydrocarbons, aromatics and ethers. The Stevens rearrangement proceeds with greater velocity in less polar solvents in the order $\text{MeOH} < \text{EtOH} < i\text{-PrOH} < n\text{-PrOH}$.⁴² The rearrangement can be run in a vacuum; in these cases,^{14,17,34} the quaternary ammonium hydroxide is used, with the counter ion acting as an in situ base.

Bases used include carbonate,⁴⁸ hydroxide,²⁶ alkoxide,⁹ hydride,³⁷ metal amide,⁴⁹ and organolithium.²⁷ Where the 'onium salt is present as the hydroxide, P_2O_5 or H_2SO_4 can be used to generate the ylid by dehydration. The combined effects of varying the base and solvent can be seen in the rearrangement of a benzyltetrahydroquinolinium salt. Phenyllithium in diethyl ether produced a Stevens to Sommelet product ratio of 40:1; sodium amide in ammonia produced a product ratio of 2:1. In the former case, the total yield was 87%; in the latter, 25%.⁵⁰

Stevens rearrangements have been carried out at temperatures ranging from -70°C to 200°C .⁸ The lower temperatures are generally used for the Sommelet rearrangement, and those higher for Stevens rearrangements. Since the transition state for the Stevens rearrangement has a higher ΔH^\ddagger , at higher temperatures, the Stevens rearrangement predominates.^{26,51} A recent study has linked the percent radical pathway with the temperature of reaction.⁵²

Mechanism. The mechanism of the Stevens rearrangement isn't known, and there may be more than one. Since the last reviews, a number of important studies with bearing on the mechanism have been published. Recent advances in the study of radical intermediates in chemical reactions and the advent of orbital symmetry conservation awareness have shed new light on the rearrangement. A discussion of the mechanistic hypotheses and the bearing recent research has on them might be fruitful.

Two basic types of mechanism--dissociative and non-dissociative--have been proposed. Five mechanisms seem to have received the most attention, and are therefore presented in Eqs. 12-16. The recent recognition of the



possibility of dual pathways in Stevens rearrangements makes consideration of these mechanisms especially worthwhile.

The initial observations which inspired mechanistic postulations were those of substituent effects (*vide supra*),⁴¹⁻⁴³ intramolecularity,¹⁹⁻²² and retention of configuration in the migrating species.²³ Substituent effects pointed to the ion-recombination pathway⁴¹ (Eq. 12), and the observed intramolecularity and retention suggested an intramolecular displacement or tight ion-pair mechanism.

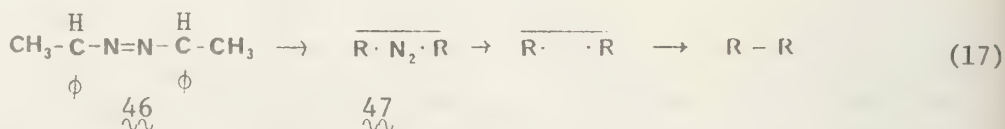
The recent recognition of the importance of orbital symmetry conservation³¹ and the development of CIDNP⁵⁴ are germane to the Stevens rearrangement. Symmetry rules suggest that the rearrangement cannot be both concerted and proceed with retention of configuration;⁵³ this would rule out an Eq. 15 mechanism. The observation of CIDNP--Chemically Induced Dynamic Nuclear Polarization--in a Stevens rearrangement⁵⁵ constituted evidence that Stevens precursors were radical in nature, and inspired renewed interest in the rearrangement.

CIDNP is seen as the enhanced absorbance or emission in nmr spectra when unpaired electron density influences nuclear spin state populations, and is observed for species whose predecessors have been radical generating reagents.^{56,57} Though the absence of CIDNP does not preclude the presence of radicals, and though its observation does not prove that a significant portion of a reaction proceeds through radical intermediates, it is still very useful.

The evidence for a radical mechanism is impressive. A number of CIDNP studies have been performed,^{10,45,59} and claims for percent radical nature in the rearrangement vary from 0%¹⁵ to 100%.⁴⁰ Proposed radical pathways

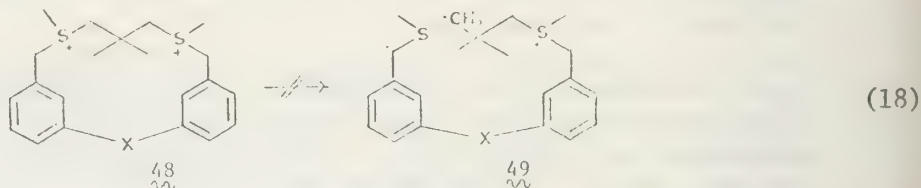
seem to follow that of Eq. 16. A chain reaction mechanism has been discounted since both the intramolecularity (where intramolecularity and CIDNP have been investigated in the same system),²¹ and CIDNP theory⁶⁰ argue against it.

The retention of optical purity and a proposed radical mechanism are not mutually contradictory.^{61,62} The current model for a Stevens rearrangement specifies cage recombination⁷¹ on a time scale which is faster than that for radical rotation or tumbling.^{59,62} The radical pair can have and retain optical activity until a member rotates or leaves the cage;⁶⁴ this process in the Stevens rearrangement is facilitated by increases in temperature and solvent viscosity.⁶³ Unlike the decomposition of diazo-bis- α -phenylethane (46 in Eq. 17)⁶⁴ where the optical activity was lost, homolysis



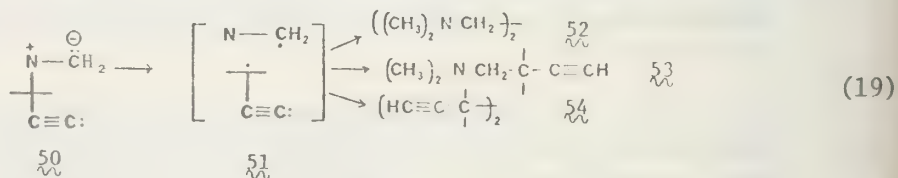
in Stevens rearrangements results in the radical pair unseparated by a molecule (N_2 in Eq. 17) which can diffuse out leaving a hole in which a radical can rotate. Radical mechanisms are consequently not contraindicated by the observation of retention.

Other evidence supporting radical intermediates is the failure of a rearrangement in the absence of substrate features capable of stabilizing both the ylid and the migratory radical, as in the attempted [1.5] cyclophane synthesis (Eq. 18)⁶⁶ where the capacity for both types of stabiliza-



tion seems absent. Similarly, benzyltrimethylammonium bromide gives poor Stevens yields, whereas dibenzyltrimethylammonium bromide does not.⁴⁷ Additional evidence comes from the preference of tertiary over primary migrations¹⁷ and the greater readiness of 1-adamantyl over 2-adamantyl migration²³ which is consistent⁷⁰ with the work of Tabushi on adamantyl radicals.⁶⁷

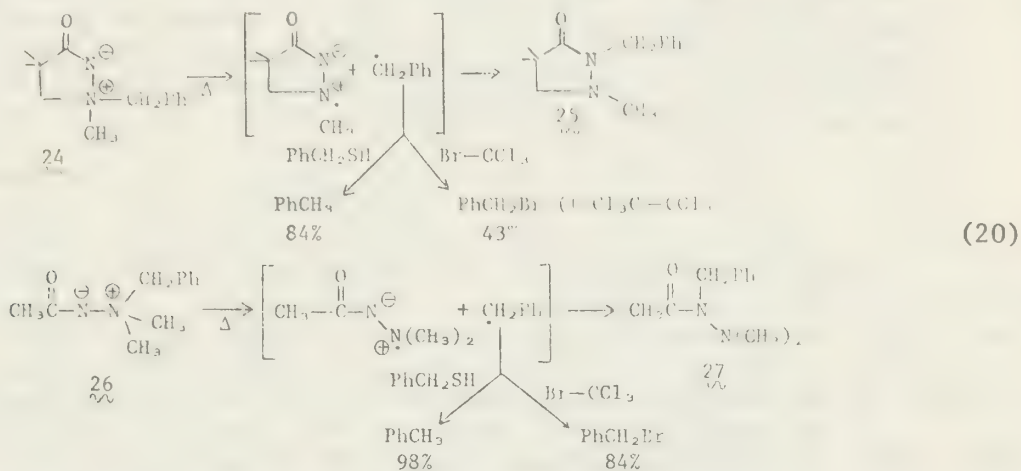
The observation of migratory group dimers^{68,69} and of all three possible coupling products (52-54) arising from an Eq. 16 mechanism (Eq. 19),¹⁸



constitutes additional evidence for a radical mechanism. Side products arising from radical coupling in a sulfonium analog have also been observed.⁷ Radicals are believed to occur in analogous⁵⁴ Meisenheimer, Wittig, and Martynoff rearrangements.^{7,70}

There remains, however, reason to consider other mechanisms. Recent work indicates that the Stevens rearrangement may not proceed entirely by a radical mechanism. There appears to be only one report of a quantitative

study of CIDNP⁵⁹ in a Stevens rearrangement and recent work supports the possibility of dual pathways therein.^{58,59} Warnings against over-interpretation of CIDNP phenomena have been issued;⁵⁸ CIDNP may be observable for escape products only.⁶² In a radical trapping experiment on aminimides, Benecke and Wikel⁴⁰ (Eq. 20) have concluded that the Stevens rearrangement



is entirely radical in nature after trapping 98 mol% of benzyl radicals with benzyl thiol. They have taken the lower trapping mol% for the cyclic aminimide **24** as an indication of tighter radical pairing due to relief of steric strain (vide supra, Eq. 10). The high yield of hexachloroethane was taken as proof that benzyl radicals, not anions, were the abstracting species when bromotrichloromethane was used. In a quantitative CIDNP study, Dolling⁵⁹ has calculated that in the reaction of **2** to **3** (Eq. 2), only 20% of **3** is formed from radical precursors. In the rearrangement of neopentyltrimethylammonium iodide, Pine¹⁵ failed to detect any CIDNP at all. Thus, though no proof of a double mechanism exists, the observation of only partial radical character suggests the possibility of simultaneous radical and non-radical mechanisms. Recent work has prompted a reexamination of some mechanisms which may have been discounted too hastily after the CIDNP discovery.

One possibility is the sequential concerted mechanism (Eqs. 13 and 14). In the case of a [1,4] shift followed by a concerted (forbidden) [1,3] shift, Pine⁷¹ has discounted this scheme because an independent synthesis of **38** followed by treatment under Stevens conditions failed to produce **39**. The Jemison scheme⁷² (**34**-**36**) has been discounted by Baldwin⁴⁵ who succeeded in effecting the thermal [3,1] isomerization, but observed that it took ten times as long as the overall rearrangement.

There has also been a reconsideration of the concerted mechanism (Eq. 15). Though Schöllkopf⁷ argues against it, the calculations of Dewar⁵³ indicate that it is energetically feasible. If orbital symmetry considerations take second place to thermodynamic ones,¹⁰ for very exothermic reactions where the transition state resembles the ground state, the differences between aromatic and antiaromatic³¹ become insignificant. MINDO/3⁷³ calculations⁵³ indicate that tetramethylammonium bromide could rearrange concertedly.

The ion-recombination mechanism (Eq. 12) has been little mentioned since the advent of CIDNP. Pine¹⁵ suggests that the rearrangement of neopentyltrimethylammonium iodide occurred via an ion-pair, since he failed to observe any evidence for radicals. An ion-pair mechanism appears to offer no advantages in explaining stereochemical features of the rearrangement,⁶² and Pine⁷¹ argues against the feasibility of two dissociative

mechanisms operating at the same time. This mechanism remains an alternative, though.

The Stevens rearrangement remains a poorly understood reaction. Recent evidence suggests that radicals are involved in the Stevens rearrangement, but where and how much is not clear. A determination of the variables and parameters which can direct this rearrangement along various predictable pathways will not only provide information of chemical interest, but will be useful in synthetic applications as well.

BIBLIOGRAPHY

1. T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. MacNicol, *J. Chem. Soc.*, 3193 (1928).
2. F. Heydenreich *et al.*, *Israel J. Chem.*, 10, 293 (1972).
3. J. Meisenheimer, *Chem. Ber.*, 52, 1667 (1919).
4. G. Wittig and L. Lohman, *Justus Liebigs Ann. Chem.*, 550, 260 (1942).
5. S. Wawzonek and E. Yeakey, *J. Am. Chem. Soc.*, 82, 5718 (1960).
6. U. Schöllkopf, *Angew. Chem.*, Int. Ed. Engl., 9, 763 (1970).
7. U. Schöllkopf, *Ind. Chim. Belge.*, 36, 1057 (1971).
8. A. R. Lepley and A. G. Giumanini in "Mechanisms of Molecular Migrations," Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1971, p. 297.
9. S. H. Pine, *Org. React.*, 18, 403 (1970).
10. H. Iwamura, M. Iwamura, T. Nishida, M. Yoshida, and J. Nakayama, *Tetrahedron Lett.*, 63 (1971).
11. Y. Hata and M. Watanabe, *Tetrahedron Lett.*, 4659 (1972).
12. D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N.Y., 1965, pp. 20-22, 223-229.
14. B. L. Adams and P. Kovacic, *J. Org. Chem.*, 39, 3090 (1974).
15. S. H. Pine, B. A. Cattos, and F. G. Yamagishi, *J. Org. Chem.*, 35, 3663 (1970).
16. W. K. Musker, *J. Org. Chem.*, 32, 3189 (1967).
17. B. L. Adams, J.-H. Liu, and P. Kovacic, *Tetrahedron Lett.*, 429 (1974).
18. G. F. Hennion and M. J. Shoemaker, *J. Am. Chem. Soc.*, 92, 1769 (1970).
19. T. S. Stevens, *J. Chem. Soc.*, 2107 (1930).
20. A. Campbell, A. H. Houston, and J. Kenyon, *J. Chem. Soc.*, 93 (1947).
21. J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, *Chem. Commun.*, 576 (1970).
22. E. Grovenstein and G. Wentworth, *J. Am. Chem. Soc.*, 89, 1852 (1967).
23. J. H. Brewster and M. W. Kline, *J. Am. Chem. Soc.*, 74, 5179 (1952).
24. R. K. Hill and T.-H. Chan, *J. Amer. Chem. Soc.*, 88, 866 (1966).
25. H. Joshua, R. Gans, and K. Mislow, *J. Am. Chem. Soc.*, 90, 4884 (1968).
26. A. G. Giumanini, C. Trombini, G. Lercker, and A. R. Lepley, *J. Org. Chem.*, 41, 2189 (1976).
27. T. Kametani, S.-P. Huang, A. Ujiie, M. Ihara, and K. Fukumoto, *Heterocycles*, 4, 1223 (1976).
28. E. Vilsmaier, K. H. Dittrich, and W. Sprugel, *Tetrahedron Lett.*, 3601 (1974).
29. M. Sommelet, *Compt. Rend.*, 205, 56 (1937).
30. S. Mageswaran, W. D. Ollis, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 656 (1973).
31. R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Academic Press, New York, N.Y., 1971, pp. 114-132.
32. D. A. Archer, *J. Chem. Soc., C*, 1329 (1971).
33. R. F. Smith *et al.*, *J. Org. Chem.*, 39, 2036 (1974).
34. J. L. Fry, M. G. Adlington, R. C. Badger, and S. K. McCullough,

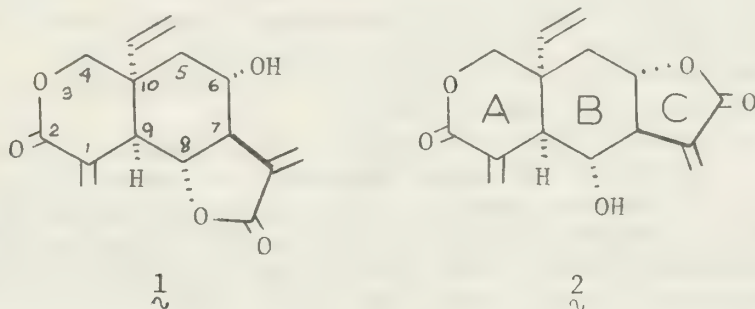
35. Y. Sato, T. Toyo'oka, T. Aoyama, and H. Shirai, J. Chem. Soc., Chem. Commun., 640 (1975).
36. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N.Y., 1968, p. 759.
37. J. R. Davy and J. A. Reiss, Tetrahedron Lett., 3639 (1972).
38. P. A. Greico, M. Meyers, and R. S. Finkelhor, J. Org. Chem., 39, 119 (1974).
39. V. Boekelheide and P. H. Anderson, Tetrahedron Lett., 1207 (1970).
40. H. P. Benecke and J. H. Wickel, Tetrahedron Lett., 3479 (1971).
41. J. L. Dunn and T. S. Stevens, J. Chem. Soc., 279 (1934).
42. T. Thomson and T. S. Stevens, J. Chem. Soc., 55 (1932).
43. J. L. Dunn and T. S. Stevens, J. Chem. Soc., 1926 (1934).
44. R. W. Jemison et al., Chem. Commun., 1201 (1970).
45. J. E. Baldwin, J. E. Brown, and R. W. Cordell, Chem. Commun., 31 (1970).
46. A. R. Lepley and R. H. Becker, J. Org. Chem., 30, 3888 (1965).
47. K. P. Klein, D. N. VanEnam, and C. R. Hauser, J. Org. Chem., 32, 1157 (1967).
48. R. W. C. Cose, A. M. Davies, W. D. Ollis, C. Smith, and I. O. Sutherland, Chem. Commun., 293 (1969).
49. Alkali metal amides can be used where Sommelet processes do not compete (Ref. 18).
50. G. Greth, H. L. Lee, and M. R. Uskoković, Tetrahedron Lett., 1937 (1969).
51. H. Zimmerman in "Molecular Rearrangements," Vol. I, P. deMayo, Ed., Wiley, New York, N.Y., 1963, pp. 378-382.
52. W. D. Ollis, I. O. Sutherland, and Y. Thebtaranonth, J. Chem. Soc., Chem. Commun., 654 (1973).
53. M. J. S. Dewar and C. A. Ramsden, J. Chem. Soc. Perkin Trans. 1, 1839 (1974).
54. A. R. Lepley in "Chemically Induced Magnetic Polarization," A. R. Lepley and G. L. Closs, Ed., Wiley, New York, N.Y., 1973, pp. 323-384.
55. H. R. Lepley, J. Am. Chem. Soc., 91, 1237 (1969).
56. S. H. Pine, J. Chem. Educ., 48, 99 (1971).
57. J. W. Wilt in "Free Radicals," J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, pp. 333-501.
58. J. Jacobus, Chem. Commun., 709 (1970).
59. U. H. Dolling, G. L. Closs, A. H. Cohen, and W. D. Ollis, J. Chem. Soc., Chem. Commun., 545 (1975).
60. H. Fischer, Ind. Chim. Belge., 36, 1054 (1971).
61. E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962, p. 383.
62. H. R. Ward in "Free Radicals," J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, pp. 265-268.
63. W. D. Ollis, M. Rey, I. O. Sutherland, and G. L. Closs, J. Chem. Soc., Chem. Commun., 543 (1975).
64. F. D. Greene, M. A. Berwick, and J. C. Stowell, J. Am. Chem. Soc., 92, 867 (1970).
65. T. Koenig and J. W. Owens, J. Am. Chem. Soc., 95, 8484 (1973).
66. N. Finch, C. W. Gemenden, and B. P. Korzun, J. Org. Chem., 41, 2509 (1976).
67. I. Tabushi, Y. Aoyama, S. Kojo, K. J. Hamuro, and Z. Yoshida, J. Am. Chem. Soc., 94, 1177 (1972).
68. U. Schöllkopf, G. Osterman, and J. Schossig, Tetrahedron Lett., 2619 (1969).
69. U. Schöllkopf, U. Ludwig, G. Osterman, and M. Patsch, Tetrahedron Lett., 3415 (1969).
70. D. G. Morris, Ind. Chim. Belge, 36, 1054 (1971).
71. S. H. Pine and J. Chenney, J. Org. Chem., 40, 870 (1975).
72. R. W. Jemison and W. D. Ollis, Chem. Commun., 294 (1969).
73. MINDO/3 (Ref. 53) is an improved version of the MINDO semi-empirical SCF MO method.

SYNTHETIC STUDIES TOWARDS (±)VERNOLEPIN AND (±)VERNOMENIN,
TWO NOVEL ELEMANOLIDE DILACTONES

Reported by William R. Baker

February 24, 1977

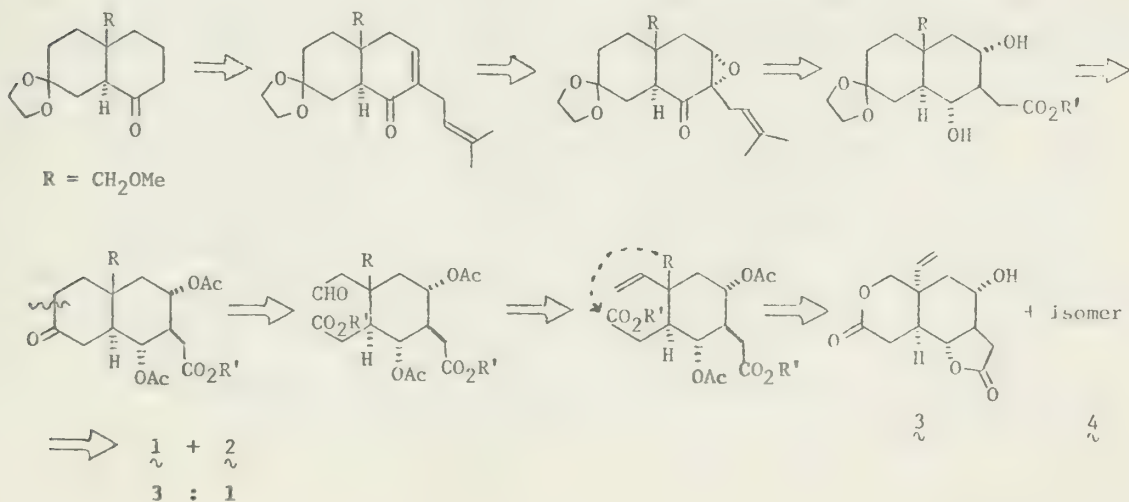
Vernolepin (1) and vernomenin (2), highly functionalized elemanolide dilactones, are major constituents of *Vernonia hymenolepis*.¹ Vernolepin shows significant activity *in vitro* against cells from human carcinoma of the nasopharynx and *in vivo* activity against the Walker intramuscular carcinosarcoma 256 in rats at 12 mg/Kg.^{1,2} Vernomenin is biologically inactive. It is postulated that the biological activity results from Michael addition of biologically important sulfhydryl groups to the α,β unsaturated system.^{3,9} These tumor inhibitory properties and novel structural features have stimulated a great deal of synthetic activity.



A successful synthesis must solve three stereochemical problems: (1) assemblage of a *cis*-3-oxa-2-decalone ring system with an angular vinyl group at carbon 10, (2) α hydroxylation at carbons 6 and 8, and (3) introduction of an acetic acid unit at carbon 7 *trans* to both hydroxyl groups. Two laboratories have reported total syntheses of vernolepin and vernomenin.^{4,5,10} Three other groups have presented partial syntheses of strategic intermediates.^{6,7,8}

An efficient solution to the vernolepin skeleton was realized by Grieco (Scheme I). α epoxidation of the substituted enone and dissolving metal reduction, with a proton source, affords the *cis* diol. Ozonolysis of the double bond produces the β acetic acid unit.

Scheme I



Transformation of the trans-fused decalin to the cis isomer completes the synthetic exercise. Oxidative cleavage of the C2-C3 bond affords two appendages differing in oxidation state at the terminal carbons. Carbons 3 and 4 become the angular vinyl. The hydroxymethyl joins the C2 acyl group to give the δ -lactone. Hydrolysis and γ -lactone formation gives a mixture of prevernolepin (3) and prevernomenin (4), which are converted to the title compounds in a 12% yield, in a ratio of 3 to 1, respectively.

BIBLIOGRAPHY

1. S. M. Kupchan, R. J. Werner, D. Werner, A. Karim, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, 90, 3596 (1968).
2. S. M. Kupchan, R. J. Hemingway, D. Werner, and A. Karim, *J. Org. Chem.*, 34, 3903 (1969).
3. S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Medicinal Chem.*, 14, 1147 (1971).
4. P. A. Grieco, Mugio Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, 98, 1612 (1976).
5. S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, 98, 3038 (1976).
6. J. A. Marshall and D. E. Seitz, *Syn. Commun.*, 4, 395 (1974).
7. K. E. Harding, "Synthetic Approach to the Vernolepin Skeleton," 172nd A. C. S. National Meeting, San Francisco, August 29, 1976.
8. (a) C. G. Chavdarian, S. L. Woo, R. D. Clark, and C. H. Heathcock, *Tetrahedron Lett.*, 1769 (1976); (b) P. M. Wege, R. D. Clark, and C. H. Heathcock, *J. Org. Chem.*, 41, 3144 (1976); (c) R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, 41, 1396 (1976).
9. For reviews of α -methylenelactone synthesis, see (a) P. A. Grieco, *Synthesis*, 67 (1975); (b) R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, 5, 245 (1975).
10. S. Danishefsky, P. Schuda, and K. Kato, *J. Org. Chem.*, 41, 1081 (1976).

A MOLECULAR ORBITAL DESCRIPTION OF STERIC ATTRACTION

Reported by Charles W. Hutchins

March 3, 1977

The geometrical and conformational preferences of molecules have been effectively rationalized by the concept of steric effects.¹ For example, the greater stability of trans-2-butene over its cis isomer is generally attributed to the relief of steric strain between the methyl groups.² Molecules contradicting this trend have been difficult to explain;³ cis-difluoroethylene is 930 cal/mol more stable than the trans isomer,⁴ and various vinyl ethers prefer an apparently more crowded structure.⁵ This account will concentrate on the attempt of the molecular orbital theory of non-bonded attraction to explain those and other instances of unexpected stability.

Introduction. Two important orbital interactions are considered in the molecular orbital (MO) theory.⁶ Interaction between two filled orbitals, ψ on atom i and ϕ on atom j , leads to four-electron destabilization ($\Delta E^{(4)}$) given by Eq. 1. This destabilization increases as the overlap integral, S_{ij} ,

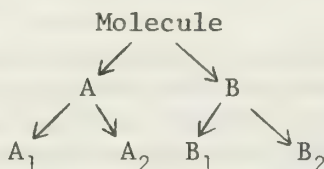
$$\Delta E^{(4)} = \frac{4S_{ij}^2}{1-S_{ij}^2} (\epsilon_0 - k) \quad (1)$$

and mean energy, ϵ_0 , increase.⁷ k is an energy constant.⁸ The second type of interaction, between a filled MO, ψ_i , and a vacant MO, ϕ_k , leads to two-electron stabilization (Eq. 2).

$$\Delta E^{(2)} = \frac{S_{ik}^2 (k - \epsilon_i)^2}{\epsilon_i - \epsilon_k} \quad (2)$$

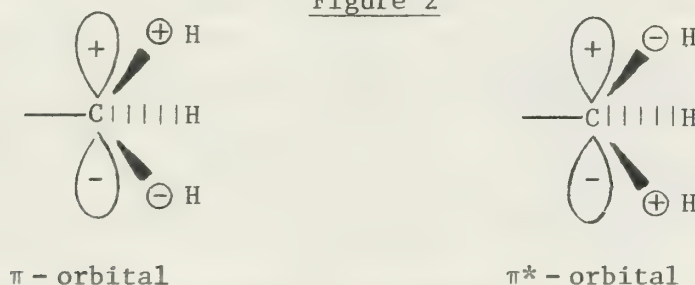
The molecular orbitals are constructed by the recombination of molecular fragments⁹ and their respective orbitals. These fragments are obtained by structural surgery of the molecule (Figure 1). By sequential combination of basic fragments, the MOs of a specific molecular geometry may be defined.

Figure 1



The concept of the π -type orbitals of a methyl group^{9,10} is central to this treatment. The orbitals, shown in Figure 2, may be considered to arise

Figure 2



from the combination of the 1s atomic orbitals of the hydrogens with a p_z orbital on carbon, with one hydrogen in the nodal plane. This gives a π -bonding and a π -antibonding type orbital.

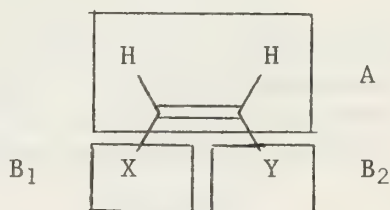
Disubstituted Ethylenes. Investigations^{3d,11} of the thermal equilibrium of geometrical isomers indicate that many halo- and alkoxy- substituted ethylenes (Table 1) have a preferred cis configuration, although this isomer

Table 1. Equilibrium Composition of Cis and Trans¹²
Isomers in $XHC=CHY$ Molecules

X,Y	% Cis at Equil Temp	Temp (°C)
F,F	63	200
F,Cl	70	200
F,Br	70	200
F,I	94	200
Cl,Cl	61	185-275
Br,Br	50	225
OMe,OMe ^{11d}	75	175

is ostensibly more crowded than the trans. In 1,2-difluoroethylene, a representative of this class, the molecular orbitals are formed by the combination of three fragments¹³ (Figure 3). The orbitals resulting from the

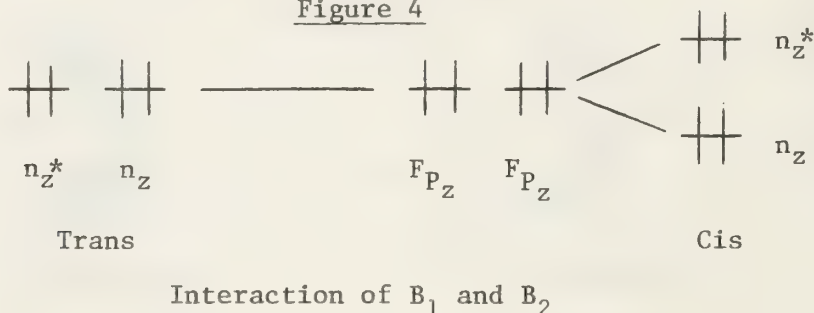
Figure 3



union of the B_1 and B_2 fragments are evaluated. The interaction of one fluorine lone pair orbital with another depends on the overlap integral and results in a pair of group orbitals. Then the interaction of these lone pair group orbitals with the A fragment orbitals, the ethylene π and π^* orbitals, are analyzed.

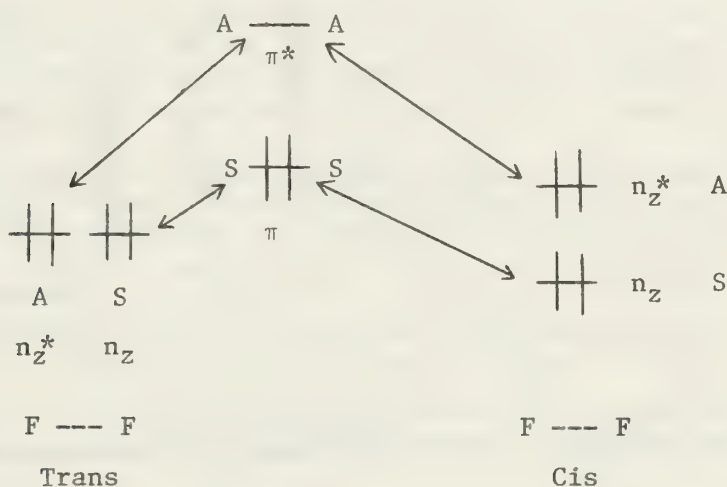
The interaction between B_1 and B_2 (Figure 4) results in four-electron destabilization ($\Delta E^{(4)}$). The overlap of the fluorine lone pairs in the

Figure 4



trans isomer is near zero and hence the orbitals remain degenerate. The larger overlap in the cis isomer is sufficient to give two non-degenerate filled orbitals, n_z and n_z^* . Inclusion of the A fragment, the π -bond of the ethylene, results in the addition of two other interactions (Figure 5).

Figure 5



Interaction of A and B Fragments

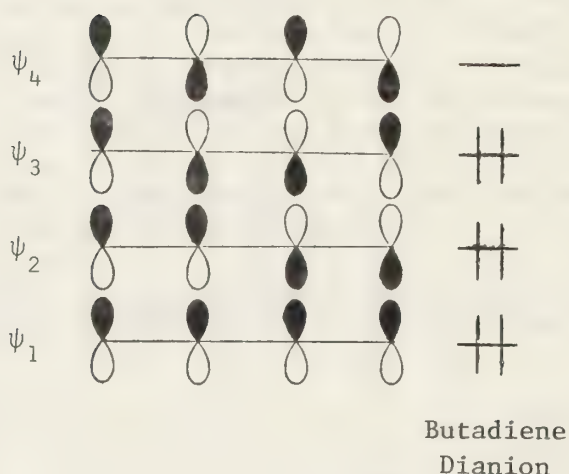
Arrows indicate important interactions; A and S refer to symmetry of orbitals.

The interaction of the filled orbitals, n_z of the lone pair group orbitals and the π orbital of the ethylene, leads to four-electron destabilization. The magnitude of the destabilization will be less for the cis isomer since the mean energy, ϵ_0 , is more negative. The two-electron stabilization, from the interaction of the filled n_z^* and vacant π^* of the ethylene, favors the cis structure owing to the smaller energy separation of these orbitals. The results of *ab initio* calculations by Epiotis⁸ indicate that the stabilization energy favoring the cis form is greater than the destabilization energy. This is manifested by the relative stability of the isomers.

The electronegativity of fluorine causes a large energy difference between the n_z orbitals of fluorine and the π orbitals of the ethylene. As less electronegative atoms are substituted, it is anticipated that the energy gap will decrease and the cis configuration will be more favored. The relative stability of the cis isomer increases as one goes from the difluoro to dimethoxy compounds (Table 1).

An analogous method of interpreting the experimental observations is by comparison of the disubstituted olefins with the orbitals of butadiene (Figure 6). The six electrons in the olefin, two from each fluorine and two from the ethylene π -bond, will fill ψ_1 , ψ_2 and ψ_3 of butadiene. The ethylenes are thus isoelectronic with the butadiene dianion. Photoelectron spectroscopy¹⁴ has shown that the highest occupied molecular orbital (HOMO) of *cis*-difluoroethylene appears similar to ψ_3 with the lone pair orbitals localized mainly on the fluorine and little mixing into the filled π orbital of the double bond. Since ψ_3 is filled, there results some degree of 1,4 bonding and net stabilization of the cis configuration.

Figure 6



Polyenes. The non-bonding molecular orbital (NBMO) of the pentadienyl π -system has the structure in Figure 7. Introduction of one or two electrons

Figure 7



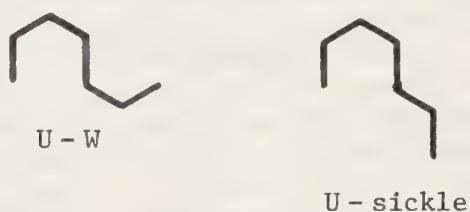
in this orbital would be expected to stabilize^{10b} a structure with atoms 1 and 5 brought close together. This 1,5 bonding interaction would favor the U-form (Figure 8) over the other possible configurations. Similar

Figure 8



bonding is present in the heptatrienyl anion, thus favoring the U-W and U-sickle forms (Figure 9). Promoting electrons into the NBMO of the

Figure 9



pentadienyl system by excitation of the cation or formation of the radical or anion would increase 1,5 bonding and consequently stabilize the U-form. From studies of the base-induced isomerization of hexahydronaphthalenes Bates *et al.*¹⁵ concluded that U-shaped pentadienyl systems are about 2-5 kcal/mole more stable than other configurations.

The *cis* isomer of the methyl-substituted allyl anion is favored over the *trans* because of the NMR spectrum of methyl allyl lithium indicates an 85:15 *cis:trans* ratio^{16a}. The π -type orbitals of the methyl group interact with the HOMO of the anion; the resulting orbital is similar to the pentadienyl NBMO. Similar NMR results have been obtained for the 1-methylpentadienyl^{15b,17} and 1-methylheptatrienyl¹⁸ analogues. Since only the ψ_2 orbital of the pentadienyl system will be filled in the methyl-substituted allyl cation, 1,5 interactions will destabilize the *cis* configuration, leading to greater stability of the *trans* configuration. The NMR evidence showing *trans-trans*-1,3-dimethylallyl cation¹⁹ to be the most stable of the three isomeric cations is in concert with theory.

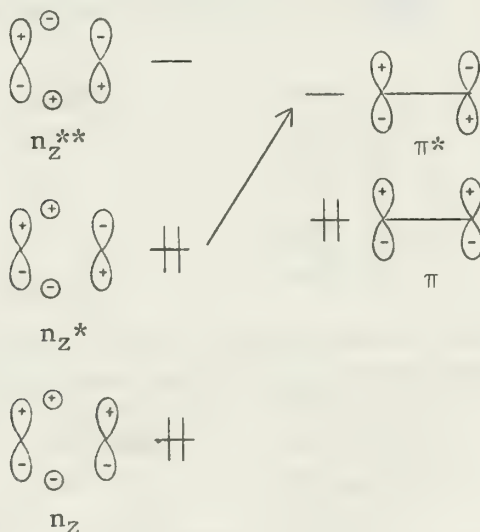
1-Substituted Propenes.²⁰ The relative stability and other conformational details of *cis*-1-substituted propenes may be rationalized by the fragment approach described earlier. Examples illustrating the preference for *cis*-substituted propenes are listed in Table 2. Interaction of the

Table 2. Equilibrium Composition of *Cis* and *Trans* Isomers of 1-Substituted Propenes

Compound	% <i>Cis</i> at Equil	Temp
$\text{CH}_3\text{CH}=\text{CHMe}$	71	25°
$\text{CH}_3\text{CH}=\text{CHOPh}$	65	--
$\text{CH}_3\text{CH}=\text{CHCl}$	76	30°
$\text{CH}_3\text{CH}=\text{CHBr}$	68	0 - 100°

π -type methyl orbitals gives rise to a set of composite orbitals which interact with the ethylene π MOs. Interaction of the n_Z^* orbital with the π^* orbital in Figure 11 results in attraction between the methyl group and

Figure 11. Interaction of lone pair - methyl orbitals with ethylene orbitals.



the 1-substituent. Epitotis'²⁰ calculations are in agreement with the qualitative theory.

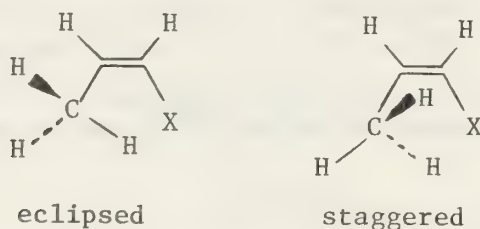
The lower barrier for rotation of the methyl group²¹ of the *cis* isomer (Table 3) is anticipated by the theory and calculations.²⁰ The energy

Table 3. Relationship Between Geometric and Rotational Isomerism in 1-Substituted Propenes

Molecule	% Cis at Equil	Rotational Cis	Barrier (kcal/mole) Trans
$\text{CH}_3\text{CH}=\text{CHF}$		1.06	2.20
$\text{CH}_3\text{CH}=\text{CHCl}$	76	0.62	2.17
$\text{CH}_3\text{CH}=\text{CHBr}$	68	0.23	2.12
$\text{CH}_3\text{CH}=\text{CHCN}$	57	1.40	2.10

barrier is the difference between the staggered and eclipsed conformations (Figure 12). Through space interactions between the methyl and substituent

Figure 12



orbitals are not present in the trans form. The barrier will thus be determined by the same factors affecting the rotational barrier in propene. In the cis conformation, both the staggered and eclipsed conformations are stabilized by interaction of the methyl π -type orbitals with the heteroatom p orbital, thus lowering the energy barrier.

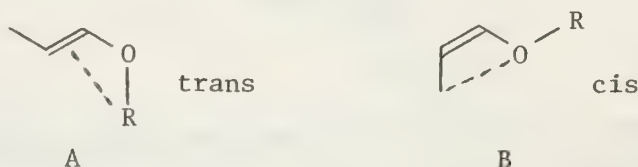
Okuyama *et al.*^{11b} have found that the configuration of the alkoxy group in 1-alkoxypropenes shifts in favor of the more crowded cis isomer as the alkyl group becomes larger (Table 4). When R is small (methyl),

Table 4. Trans - Cis Equilibrium Ratios (K) for $\text{CH}_3\text{CH}=\text{CHOR}$

R	K
CH_3	1.03
CH_2CH_3	0.72
$\text{CH}(\text{CH}_3)_2$	0.37
$\text{C}(\text{CH}_3)_3$	0.30

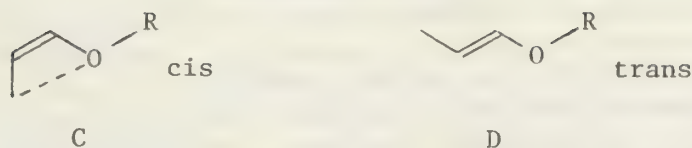
one compares the configurations A and B (Figure 13). The stability of A is a consequence of the relative strengths of the two types of non-bonded

Figure 13



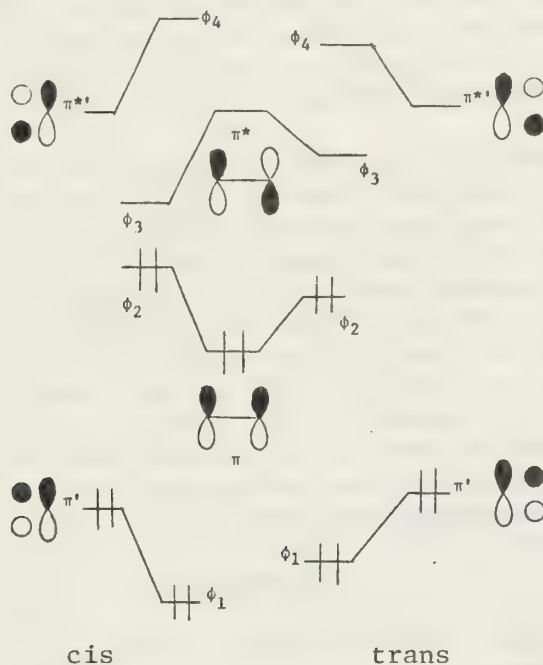
attractions. As the alkyl group becomes bulkier, a comparison of structures C and D (Figure 14) reveals that only the cis isomer possesses the non-bonded attraction.²⁰

Figure 14

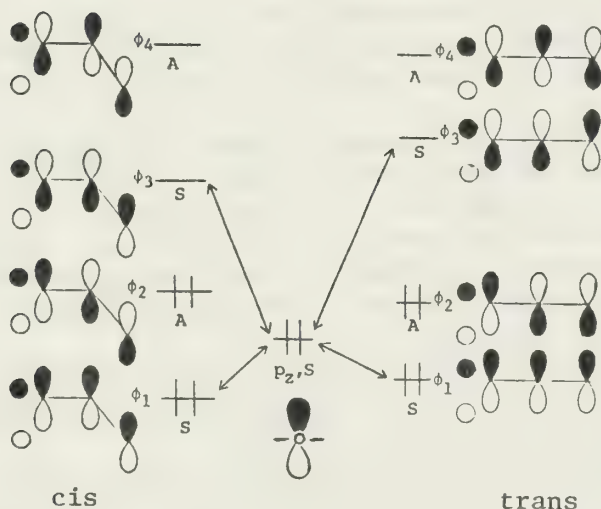


Methyl Vinyl Ether.²² The combination of the fragments and examination of the orbital interactions in Figure 15 yields the molecular orbitals of the ether. The larger destabilization of the cis isomer from the vinyl-

Figure 15



(a) Interaction of methyl π -type orbitals with vinyl orbitals



(b) Interaction of vinyl-methyl group orbitals with oxygen lone pair

methyl interaction of filled orbitals will be offset by the four-electron destabilization of the trans form. The destabilization of the trans isomer is due to the larger p_z - ϕ_1 interaction. The smaller energy difference between the filled and unfilled orbitals, p_z and ϕ_3 , will cause the two-electron stabilization to favor the cis conformation. Ab initio calculations²² are in agreement with Owen's experiments⁵ showing the planar cisoid conformation is the more stable.

Non-bonded attractions have been proposed¹³ to account for the "gauche effect," the preference of 1,2-disubstituted ethanes for the gauche conformation.²³ The preferential stability of the gauche conformation results from the interaction of the lone pair composite orbitals with the unfilled σ^* orbital. Other studies²⁴ in which non-bonded attractions have been considered include the syn-transition state for the S_N2' reaction,²⁵ the recombination of ethyl cations with ethyl anions,²⁶ and the preferred syn addition of unsymmetrical carbenes to cis olefins.²⁷

The alternative explanations²⁸ for many of the conformational and geometrical preferences described may act in concert with orbital interactions to explain the relative stability in these examples. In the cis disubstituted ethylenes, hyperconjugation^{3c,29} has been used to account for the experimental observations. London dispersion forces,^{28c} charge separation in the transition state,²⁷ and various other theories²⁸ have been offered to rationalize the relative stability of the more crowded conformation. Steric effects will, at some point, reverse the relative stability of the cis and trans isomers.³⁰ The molecular orbital theory of non-bonded attraction is a step forward in the understanding of the thermodynamic stability of conformational and geometrical isomers which conflict with predictions based upon simple steric strain.

BIBLIOGRAPHY

1. M. S. Newman, Ed., "Steric Effects in Organic Chemistry," Wiley, New York, N.Y., 1956.
2. R. T. Morrison and R. N. Boyd, "Organic Chemistry," 3rd ed., Allyn and Bacon, Boston, Mass., 1973, p. 185.
3. (a) M. Schlosser, Bull. Soc. Chim. Fr., 455 (1971); (b) M. Schlosser, Top. Stereochem., 5, 1 (1970); (c) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962; (d) K. S. Pitzer and J. L. Hollenberg, J. Am. Chem. Soc., 76, 1493 (1954).
4. N. C. Craig, L. G. Piper, and V. L. Wheeler, J. Phys. Chem., 75, 1453 (1971).
5. (a) N. L. Owen and N. Sheppard, Trans. Faraday Soc., 60, 634 (1964); (b) N. L. Owen and H. M. Seip, Chem. Phys. Lett., 5, 162 (1970).
6. L. Salem, J. Am. Chem. Soc., 90, 543 (1968).
7. N. C. Baird and R. M. West, J. Am. Chem. Soc., 93, 4427 (1971).
8. N. D. Epiotis and R. L. Yates, J. Am. Chem. Soc., 98, 461 (1976).
9. W. L. Jorgensen and L. Salem, "The Organic Chemist's Book of Orbitals," Academic Press, New York, N.Y., 1973.
10. (a) B. M. Gimarc, J. Am. Chem. Soc., 93, 593 (1961); (b) R. Hoffmann and R. A. Olofson, J. Am. Chem. Soc., 88, 943 (1966); (c) R. Hoffmann, Pure and Applied Chem., 24, 567 (1970).
11. (a) H. G. Viehe, Chem. Ber., 93, 1697 (1960); (b) T. Okuyama, T. Fueno, and J. Furukawa, Tetrahedron, 25, 5409 (1969); (c) H. G. Viehe and E. Franchimont, Chem. Ber., 96, 3153 (1963); (d) J. T. Waldron and W. H. Snyder, J. Am. Chem. Soc., 95, 5491 (1973).
12. N. D. Epiotis, S. Sarkanen, D. Bjorkquist, L. Bjorkquist, and R. Yates, J. Am. Chem. Soc., 96, 4075 (1974).

13. N. D. Epiotis, J. Am. Chem. Soc., 95, 3087 (1973).
14. C. R. Brundle, M. B. Robin, N. A. Kuebler, and H. Basch, J. Am. Chem. Soc., 94, 1451 (1972).
15. (a) R. B. Bates, R. H. Carnighan, and C. E. Staples, J. Am. Chem. Soc., 85, 3031 (1963); (b) However, see W. T. Ford and M. Newcomb, J. Am. Chem. Soc., 96, 309 (1974).
16. (a) R. B. Bates and W. A. Beavers, J. Am. Chem. Soc., 96, 5001 (1974); (b) S. Bank, A. Schriesheim and C. A. Rowe, Jr., J. Am. Chem. Soc., 87, 3244 (1965).
17. G. J. Heizwolf, J. A. A. van Drunen, and H. Kloosterziel, Recl. Trav. Chim. Pays-Bas, 88, 1377 (1969).
18. H. Kloosterziel and J. A. A. van Drunen, Recl. Trav. Chim. Pays-Bas, 88, 1471 (1969).
19. P. v. R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfeld, J. Am. Chem. Soc., 91, 5174 (1969).
20. N. D. Epiotis, D. Bjorkquist, L. Bjorkquist, and S. Sarkanen, J. Am. Chem. Soc., 95, 7558 (1973).
21. J. P. Lowe, Prog. Phys. Org. Chem., 6, 1 (1968).
22. F. Bernardi, N. D. Epiotis, R. L. Yates, and H. B. Schlegel, J. Am. Chem. Soc., 98, 2385 (1976).
23. S. Wolfe, Accounts Chem. Res., 5, 102 (1972).
24. (a) N. D. Epiotis and W. Cherry, Chem. Commun., 278 (1973); (b) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N.Y., 1970.
25. R. L. Yates, N. D. Epiotis, and F. Bernardi, J. Am. Chem. Soc., 97, 6615 (1975).
26. R. Hoffmann, C. C. Levin, and R. A. Moss, J. Am. Chem. Soc., 95, 629 (1973).
27. (a) G. L. Closs and R. A. Moss, J. Am. Chem. Soc., 86, 4042 (1964); (b) G. L. Closs, Top. Stereochem., 3, 193 (1968).
28. (a) R. C. Bingham, J. Am. Chem. Soc., 98, 535 (1976); (b) E. Scarzafava and L. C. Allen, J. Am. Chem. Soc., 93, 311 (1971); (c) M. K. Kaloustian, J. Chem. Ed., 51, 777 (1974); (d) K. Fukui, Tetrahedron Lett., 2427 (1965).
29. M. J. S. Dewar, "Hyperconjugation," Ronald Press Co., New York, N.Y., 1962.
30. N. D. Epiotis, R. L. Yates, and F. Bernardi, J. Am. Chem. Soc., 97, 5961 (1975).

DIRECTED METALATION OF AROMATIC AND HETEROAROMATIC COMPOUNDS

Reported by Roger A. Brown

March 7, 1977

Regiospecific functionalization of mono-substituted benzene compounds has always been at least a potential problem. Classical electrophilic substitution conditions often produce mixtures of structural isomers, as well as poly-substituted products, the presence of which may make isolation of the desired product difficult or impossible. Alternatively, nucleophilic aromatic substitutions are more regiospecific, but require preparation of precursors with specific substituents.

Directed metalation^{1,2,3} is a more recently developed method for the derivatization of aromatic compounds and avoids many of these problems. It involves the use of lithium alkyls or lithium dialkylamides to deprotonate aromatics, priming them for condensation with a variety of electrophilic reagents. The recurring theme in all reactions of this type is that derivatization occurs only on atoms adjacent to a functionality already present. This limits the general utility of the reaction, but in applicable situations, the regiospecificity is generally high (although the product yield may vary from poor to excellent) and problems of contamination by products of competing side-reactions are usually minimal.

The ability to direct metalation to an ortho carbon has been reported for several functionalities: secondary and tertiary amines,² secondary and tertiary sulfonamides,² secondary^{2,4} and tertiary⁵ amides, secondary thioamides,⁶ alcohols,^{2,3} ethers,^{2,3,7} halides,^{2,8} oxazolines,⁹ imines,¹⁰ phosphoimines,¹¹ sulfones,^{3,12} and esters.¹³ Electrophilic traps have included² alkylating agents, carbonyl compounds, nitriles, isocyanates, epoxides, CO₂, D₂O, ClSi(CH₃)₃, O₂NOC₂H₅, NH₂OCH₃, and a versatile borate trap,¹⁴ among others. The reaction has been applied to various five-membered heterocyclic aromatics,^{1,3,15} most notably thiophenes;² also, ferrocenes^{2,16} have been derivatized by directed metalation techniques. In ferrocenes, use of optically active directing groups has resulted in stereospecific ring metalation.^{2,17}

In poly-substituted benzene compounds, the position of metalation depends upon the relative directing abilities of the substituents, the nature of the base, and the temperature. A complete ordering, with regard to directing ability, of the groups mentioned above remains to be done, but some trends have been noted.² Sulfonamides appear to be unsurpassed; amines and amides, though worse than sulfonamides, are better than ethers, which in turn are better than halides and the CF₃ group. Although a direct mechanistic relationship has not been demonstrated, both the position of metalation and the yield vary as if they were related to the state of aggregation of the lithium base;¹⁸ use of a less aggregated base decreases sensitivity to steric requirements in the substrate and increases the total yield of products resulting from metalation. The extent of aggregation in the base depends not only on the specific base, but also on the solvent and the inclusion or omission of a coordinating amine, such as N, N, N', N'-tetramethylethylenediamine.

One of the most useful applications of the directed metalation reaction has been in new syntheses of fused ring systems,^{2,19} proceeding by ring closure of the intermediates which are derived from electrophilic trapping of ortho-lithio species. Aromatic-annelated lactones, lactams, sultones, sultams, cyclic ethers and cyclic amines are all readily available from these intermediates through conventional chemistry.^{1,2,19}

BIBLIOGRAPHY

1. (a) W. H. Glaze, *Organometal. Chem. Rev.*, 6, 1 (1970); (b) W. H. Glaze, *ibid.*, 8, 253 (1971); (c) W. H. Glaze, *J. Organometal. Chem.*, 48, 1 (1973); (d) W. H. Glaze, *ibid.*, 68, 1 (1974); (e) D. W. Slocum, *ibid.*, 95, 1 (1975); (f) E. M. Kaiser, *ibid.*, 98, 1 (1975).
2. D. W. Slocum and D. I. Sugarman, *Adv. Chem. Ser.*, No. 130, 222-247 (1974).
3. J. M. Mallan and R. L. Bebb, *Chem. Rev.*, 69, 693 (1969).
4. (a) B. H. Bhide and N. S. Narasimhan, *Chem. Ind. (London)*, 75 (1974); (b) N. S. Narasimhan and R. S. Mali, *Synthesis*, 797 (1975).
5. (a) R. E. Ludt, J. S. Griffiths, K. N. McGrath, and C. R. Hauser, *J. Org. Chem.*, 38, 1668 (1973); (b) L. Barsky, H. W. Gschwend, J. McKenna, and H. R. Rodriguez, *ibid.*, 41, 3651 (1976); (c) P. Beak and R. A. Brown, *ibid.*, 42, in press (1977).
6. J. J. Fitt and H. W. Gschwend, *ibid.*, 41, 4029 (1976).
7. (a) R. C. Ronald, *Tetrahedron Lett.*, 3973 (1975); (b) A. C. Ranade, R. S. Mali, S. R. Bhide, and S. R. Mehta, *Synthesis*, 123 (1976).
8. D. B. Reitz, P. Beak, and R. F. Farney, presented in part at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March, 1977.
9. (a) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, 40, 3158 (1975); (b) H. W. Gschwend and A. Hamdan, *ibid.*, 40, 2008 (1975).
10. F. E. Ziegler and K. W. Fowler, *ibid.*, 41, 1564 (1976).
11. C. G. Stuckwisch, *ibid.*, 41, 1173 (1976).
12. (a) V. N. Drozd and L. A. Nikanova, *Zh. Org. Khim.*, 4, 1060 (1968); *J. Org. Chem. U.S.S.R.*, 4, 1025 (1968); (b) V. N. Drozd and L. A. Nikanova, *Zh. Org. Khim.*, 5, 325 (1969); *J. Org. Chem. U.S.S.R.*, 5, 313 (1969).
13. C. J. Upton and P. Beak, *J. Org. Chem.*, 40, 1094 (1975).
14. E. I. Negishi, A. Abramovitch, and R. E. Merrill, *J. Chem. Soc.*, C, 138 (1975).
15. (a) B. A. Tetrov, V. V. Burykin, and I. D. Sadekov, *Khim. Geterotsikl. Soedin.*, 560 (1969); *Chem. Abstr.*, 71, 124328y (1969); (b) R. G. Micetich, *Can. J. Chem.*, 48, 2006 (1970); (c) R. P. Dickinson and B. Iddon, *J. Chem. Soc.*, C, 182 (1971); (d) T. Kaufmann and A. Mitschker, *Tetrahedron Lett.*, 4039 (1973); (e) A. J. Clarke, *ibid.*, 2373 (1974); (f) D. E. Horning, *Can. J. Chem.*, 52, 2950 (1974); (g) A. Marxer and M. Siegrist, *Helv. Chim. Acta*, 57, 1988 (1974); (h) R. J. Sundberg and R. L. Parton, *J. Org. Chem.*, 41, 163 (1976); (i) D. W. Slocum and P. L. Gierer, *ibid.*, 41, 3668 (1976).
16. (a) D. J. Booth and B. W. Rockett, *J. Chem. Soc.*, C, 3341 (1971); (b) D. W. Slocum, B. P. Koonsvitsky, and C. R. Ernst, *J. Organometal. Chem.*, 38, 125 (1972); (c) D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, 36, 377 (1971); (d) D. W. Slocum and B. P. Koonsvitsky, *ibid.*, 41, 1664 (1976).
17. (a) P. B. Valkovitch, G. W. Gokel, and I. K. Ugi, *Tetrahedron Lett.*, 2947 (1973); (b) L. F. Battelle, R. Bau, G. W. Gokel, R. T. Oyakawa, and I. K. Ugi, *J. Am. Chem. Soc.*, 95, 482 (1973).
18. (a) D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, 38, 1675 (1973); (b) D. A. Shirley and T. E. Harmon, *ibid.*, 39, 3164 (1974); (c) D. W. Slocum and C. A. Jennings, *ibid.*, 41, 3653 (1976); (d) D. A. Shirley, T. E. Harmon, and C. F. Cheng, *J. Organometal. Chem.*, 69, 327 (1974).
19. (a) N. S. Narasimhan and M. V. Paradkar, *Indian J. Chem.*, 7, 536 (1969); (b) N. S. Narasimhan and M. V. Paradkar, *ibid.*, 7, 1280 (1969); (c) N. S. Narasimhan and A. C. Ranade, *ibid.*, 7, 538 (1969); (d) N. S. Narasimhan and R. S. Mali, *Synthesis*, 796 (1975); (e) N. S. Narasimhan and R. S. Mali, *Tetrahedron*, 1005 (1975).

SOLID SUPPORTS IN ORGANIC PREPARATIONS

Reported by Christopher K. VanCantfort

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Introduction. The following abstract¹ appeared in the patent literature in 1925. "Using chemical reagents on porous carriers. Acids or other reagents for nitration, sulfonation, oil purification and other reactions are mixed with a porous substance such as bone black, fuller's earth, or burnt kieselguhr. E.g., PhNO_2 may be made by treating C_6H_6 on the water bath with HNO_3 adsorbed on kieselguhr. Numerous other examples are given." Unfortunately, it was not until some forty years later that, without reference to the original patent, this phenomenon was rediscovered. Unawareness is a characteristic that still plagues this field of research and hampers the development of reagent systems. Use of high polymer supports,² on the other hand, is a much more mature, developed, and coherent area. Similarly, the use of porous supports as catalyst carriers³ has been extensively investigated. However, the history of the use of supports which are not organic high polymers (i.e. alumina, silica gel, graphite, clays, etc.) for carrying out non-catalytic organic preparations has been spasmodic and lacking direction despite the apparent success of such applications. The nature⁴ of these amorphous, colloidal, or microcrystalline supports has been elucidated to only a limited extent. This review is intended to delineate the enormous variety, potential, and advantages of using such porous supports for the purpose of accomplishing organic preparations.

Oxidations. The most extensively investigated solid-supported reaction is Fetizon's use of Ag_2CO_3 precipitated on Celite⁵ as a highly selective oxidizing agent. The reaction products⁶ have been shown to be one mole of CO_2 and H_2O along with two moles of metallic silver per mole of alcohol oxidized. The advantages of the reagent center about the incredible simplicity of the reaction procedure and work-up, absence of acidic or basic conditions and the consistently high yield obtained. The agent's remarkable selectivity⁷ has been manifested in many cases where it has been demonstrated that the preferred order of oxidation is benzylic and allylic $> 2^\circ > 1^\circ$ for alcohols.⁵ Diols⁸ in which one hydroxyl is 2° cleanly yield hydroxy carbonyls without vicinal cleavage. Oxidation of 1,4; 1,5; and 1,6 primary diols⁹ generate the corresponding lactones. Several biochemically important lactones,^{9b} including mevalonolactone, have been prepared in this way. Steroidal triols^{5,7} have been selectively oxidized, depending upon hydroxyl stereochemistry, with surprising success. Heterocyclic aromatic alcohols¹⁰ containing N, O, or S are oxidized readily in excellent yield to the corresponding carbonyl. Non-aromatic heterocycles tend to result in various cleavage products. The reagent has found use in the preparation of aldehydes deuterated and tritiated¹¹ at the carbonyl in yields not less than 80% with isotopic purity not less than 90% possessing high millimolar radioactivity. The system appears to be the reagent of choice for the oxidative coupling of hindered phenols, conversion of catechols to o-quinones and hydroquinones to quinones.¹² Oxidation of nitrogen functionalities¹³ has been investigated with moderate success, including Büchi's synthesis of the active component¹⁴ of the aroma of freshly baked bread. Azobenzenes, diazoalkanes, nitrones, and nitrile oxides were prepared in good to moderate yield from the corresponding amines, hydrazones, hydroxylamines, and aldehydic oximes, respectively. Although not an oxidative process, vicinal halohydrins¹⁵ of conformationally fixed cyclohexyl systems can specifically yield either the corresponding epoxide, non-halogenated ketone or ring

contracted aldehyde depending upon the substituents' stereochemistry. A mechanism^{16,6} for Ag_2CO_3 -Celite oxidation of alcohols that is in accord with the available evidence has been proposed.

The reagent system of CrO_3 intercalated in graphite¹⁷ has been reported to oxidize selectively 1° alcohols to aldehydes in 80-90% yield while 2° and 3° alcohols are unaffected. Isolation of product is greatly facilitated since residual reduced chromium salts remain on the graphite during the non-aqueous work-up. The reagent is commercially available under the trade name "Seloxcette" (Ventron, 50-58% CrO_3). The mechanistic picture^{18,19} has recently been clouded by the demonstration that the active reagent is really Cr_3O_8 on the surface of the graphite. Synthetic use has been restricted primarily to natural products.²⁰

Neutral, dehydrated, chromatographic alumina has been effectively used in a number of room temperature oxidations.²¹ A variety of 2° alcohols have been selectively oxidized to ketones via Oppenauer reaction with CCl_3CHO and Al_2O_3 in high yield, gram quantity preparations. Many functionalities are inert under the reaction conditions and normal Oppenauer side reactions (*i.e.* elimination, Tischenko, Cannizzaro, and aldol condensations) do not occur. This inexpensive system ideally augments the selectivity of the Ag_2CO_3 -Celite oxidation of diols.

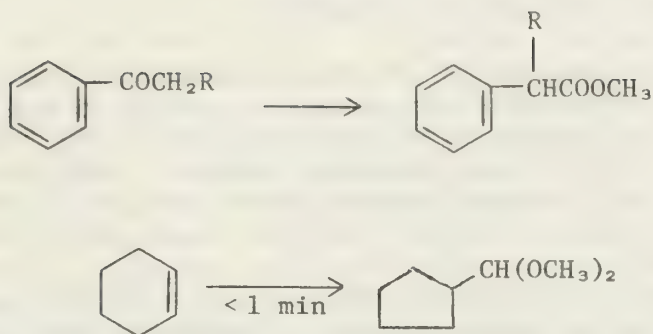
The Cannizzaro reaction²² of aldehydes has been achieved on active, neutral alumina. Tropone has been obtained in highest yield by air oxidation of tropyl azide (from the tetrafluoroborate salt) on neutral alumina.²³

A common curse of synthesis of highly sensitive natural products is that work-up conditions are occasionally more brutal than reaction conditions. Corey²⁴ has provided a good example of how this problem can be circumvented by the use of $\text{CrO}_3 \cdot 2 \text{ pyr.}$ and Celite to prepare gibberellic acid intermediates enormously susceptible to undesired aldol condensations. The same reagent, whose work-up consists of addition of powdered NaHSO_3 followed by filtration, was utilized by Andersen²⁵ who sought to avoid the chromatography of precious intermediates in his bulnesol synthesis.

In order to prevent oxidative side reactions and polymerization in the synthesis of the alkaloid salutaridine²⁶ by oxidative condensation of reticuline, it proved necessary to keep the concentration of reticuline on the surface of the oxidizing agent low and the distance between molecules large by utilization of a supplementary adsorbing surface. This dilution was achieved by addition of silica gel to the heterogeneous MnO_2 reaction mixture.

A most unusual reagent is the combination of thallium (III) trinitrate and K-10 montmorillonite clay (TTN/K-10)²⁷ used in the oxythallation of unsaturated molecules. Thus, alkyl aryl ketones oxidatively rearrange in excellent yield to α -disubstituted alkyl aryl acetates. Simple olefins oxidatively rearrange to acetals in similarly high yields (Scheme I).

Scheme I



Over twenty different supports have been investigated for these reactions and an unusual facility is displayed by the montmorillonite clays. The myriad²⁸ of known thallium (III) reactions anxiously await reinvestigation in light of these new results which are far superior to the corresponding solution reactions.

Reductions. Potassium intercalated in graphite¹⁷ (formally C_8K) has been shown to be an effective reagent for the reduction of saturated and unsaturated ketones to alcohols. The observation of pinacolic products, reversal of exo-endo product ratio in comparison to the alkali metal-alcohol reduction of camphor, and reduction of the carbon-carbon double bond of α,β unsaturated ketones all support the postulated electrochemical nature of this reagent. C_{24}K has been used to reduce and/or isomerize²⁹ both alkenes and alkynes.

Meerwein-Pondorff-Verley selective, high yield reductions^{30,31} of gram size quantities of aldehydes by isopropanol on dehydrated alumina at room temperature has been achieved. The easily isolated and purified product shows no sign of contamination by normal M-P-V side reaction products and many other functional groups are inert to the reaction conditions. Ketones are reduced more slowly than aldehydes and molecules containing both can be essentially selectively reduced. Use of α -deuterioisopropanol results in the correspondingly labelled product.

The extreme alkalinity of NaBH_4 and acidity of NaCNBH_3 reductions of ketones to alcohols often prevents their use with acid or base sensitive molecules. These difficulties have been ingeniously surmounted³² by the development of a NaBH_4 on neutral alumina (or silica gel) system that enables room temperature reduction of ketones in non-polar, non-hydroxylic solvents (i.e. dry benzene) or without any solvent at all! Yields are about 60% and the reactions follow the same steric course as NaBH_4 reductions in solution for the ketosteroids examined. Oximes treated with NaBH_4 on silica gel³³ yield the corresponding hydroxylamine (N-B) boranes which, upon treatment with HCl followed by NaOH , liberate free hydroxylamines. The intermediate hydroxylamine (N-B) boranes are themselves capable of reducing carbonyls as has been shown in the reduction of a cholestanone to the epimeric cholestanols.

Recently, the exotic reagent³⁴ potassium hydridodecacarbonyldichromate ($\text{KHCr}_2(\text{CO})_{10}$, prepared from $\text{Cr}(\text{CO})_6$, C_8K , and H_2O) has proven quite effective (60-80% yield) in selectively reducing α,β unsaturated carbonyls

to the corresponding saturated carbonyl. Most other functionalities are inert including other double bonds conjugated to the α, β unsaturation. Schiff bases are reduced to the amine.

Vapor Phase Reactions. Meerwein-Pondorff-Verley reductions and Oppenauer oxidations of carbonyls and alcohols, respectively, in the vapor phase (300°C) on activated alumina impregnated with 2.2% Na^+ have been achieved with moderate and variable success.³⁵ M-P-V reductions have also been carried out at lower temperatures³⁶ (90-160°C) without Na^+ impregnation in a study designed to analyze the relationship between Al_2O_3 calcination temperature and the extent of reduction achieved. This study concluded, in accord with the corresponding liquid phase reduction mentioned previously,³⁰ that the support activity is directly related to the number of exposed Al^{3+} Lewis acid sites and, therefore, the reduction is formally analogous to the solution M-P-V reduction mechanism. For synthetic purposes, these vapor phase reactions are restricted by the thermal stability of the substrates and products and are not as promising as the previously detailed liquid phase reactions. Vapor phase aldol condensations³⁷ of aromatic aldehydes with aliphatic aldehydes in low to moderate yield on NaOH impregnated silica gel have been described.

Substitution Reactions. Both aliphatic and aromatic substitution reactions have been executed on various supports with a variety of electrophiles or nucleophiles. Clearly, this is one example where the support plays a critical role in bringing into close proximity two interacting species. For example, tosyloxy steroids are converted in 30-60% yield to the epimeric nitrate esters³⁸ or isothiocyanates and thiocyanates³⁹ (ambident nucleophile) by interaction with the anion supported on alumina under conditions in which the anion alone has no effect. Primary, long chain aliphatic nitrates⁴⁰ are generated from the bromides in good yield (80-90%) by passing the halides over AgNO_3 -silica gel-Celite. Secondary bromides usually result in a 50/50 mixture of nitrates and olefins.

The preponderance of ortho product (p/o = 0.53) normally found in the solution nitration of aromatic compounds has been virtually reversed (p/o = 1.61) in an extensive study⁴¹ of HNO_3 nitration catalyzed by toluene-2,4-disulfonic acid supported on Celite-545. The reaction conditions have been optimized for many various supports, catalysts, temperatures, times, and component ratios. The yields are consistently greater than 90% and the catalyst support can be reused many times without affecting the results.

Graphite bisulfate ($\text{C}_{24}\text{HSO}_4^+ \cdot 2\text{H}_2\text{SO}_4$) with one equivalent of nitric acid, or graphite nitrate ($\text{C}_{24}\text{NO}_3\text{HNO}_3$) by itself, have been shown¹⁹ to be effective nitrating agents for aromatic systems.

Hydrazoic acid on acidic alumina can convert benzyl chloride to benzyl azide and β, β' -dibromosuccinate to azidofumarate⁴² at room temperature.

Bromination of aromatic compounds has been achieved with a variety of bromine supported systems. Biphenyls are selectively mono- or dibrominated⁴³ in high yield at room temperature by passing bromine gas over the substrate adsorbed on Cab-O-Sil (a porous, hydroxylated silica very similar to Celite) without an additional catalyst. The reaction is very fast (30-120 minutes) and the product mixtures obtained are virtually identical to those obtained in solution. Bromine intercalated in graphite (C_8Br)^{44, 19} has been used to monobrominate binaphthyl selectively at the four position in high yield at room temperature. Other bromine reactions (i.e.

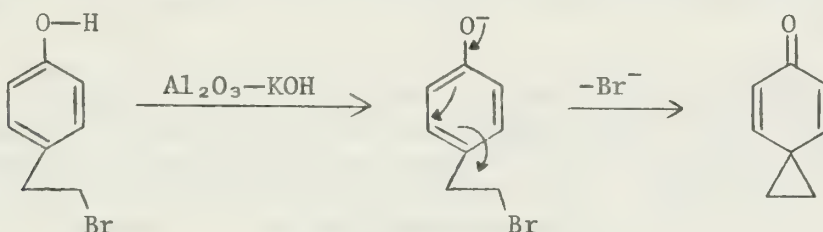
α -bromination of ketones, addition to double bonds, addition to aromatic rings, etc.) with this reagent proceed in a manner identical to solution brominations. It has not been possible to generate stable chlorine-graphite compounds, but SbCl_5 has been intercalated¹⁹ in graphite ($\text{C}_{24}\text{SbCl}_5$). This reagent can efficiently exchange chlorine for bromine in 1° or 2° bromides at room temperature whereas SbCl_5 by itself chlorinates α to the bromine under the same conditions. Antimony pentafluoride has similarly been intercalated in graphite⁴⁵ and preliminary results suggest that the reagent induces halogen exchange.

Posner⁴⁶ has carried out an interesting study of rapid, room temperature displacement reactions using neutral, dehydrated alumina doped with alcohols, thiols, and acetic acid. Methanol on alumina displaces sulfonate and sulfamate esters in 40-50% yield to form methyl ethers showing 90-95% net inversion of configuration and with no rearrangements where carbonium ions would be expected to rearrange. Alumina doped with alcohols, thiols, or acetic acid opens epoxides in one hour to the corresponding trans-2-alkoxy, trans-2-alkylthio, or trans-2-acetoxy alcohols, respectively, in 60-80% isolated yield. Here the juxtaposition of the adsorbed electrophile and nucleophile, along with the enhanced nucleophilicity of the latter, conceivably combine to permit reaction under unusually mild conditions.

Friedel-Crafts alkylation of aromatics⁴⁷ has been accomplished at room temperature using AlCl_3 -graphite (35% AlCl_3) to yield alkylated products with a significantly diminished degree of polyalkylation in comparison to the same reactions without support.

A unique intramolecular displacement⁴⁸ using aqueous KOH on alumina to convert 2-p-hydroxyphenylethyl bromide to spiro(2,5)octa-1,4-diene-3-one has been reported (Scheme II).

Scheme II



Insertion reactions. Unactivated tertiary C-H bonds remain one of the greatest obstacles to functionalization in organic synthesis. Recently, however, it has been found that such sites can be specifically hydroxylated in high yield at low temperature (-78°C) when the substrate adsorbed on silica gel is saturated with ozone.⁴⁹ The reaction is much more rapid than the corresponding solution reaction and results exclusively in monooxygenated products with virtually complete retention of configuration. Under the same conditions, secondary alcohols are oxidized to ketones and olefins can be protected by bromination, the resulting bromides being less susceptible to ozonization than the 3° C-H bonds. The sole exception⁵⁰ to date appears to be 3° cyclopropyl systems with adjacent free 2° positions. In these instances oxidation to the ketone α to the 3° site predominates.

Neutral alumina with an adsorbed monolayer of saturated fatty acids⁵¹ has been used to increase the photochlorination of the terminal positions of the substrate. The adsorbed acid can be chlorinated as a suspension in a solvent or as a dry powder. The selectivity of this procedure over homogeneous ones is attributed to the known tendency of fatty acids to adsorb in a parallel fashion perpendicular to the support surface, thereby leaving the terminal positions more freely exposed.

Alumina-KOH has been used with various haloforms to generate and insert dihalocarbenes into cyclohexene⁵² in situ at room temperature in 12-15% yield. Neutral alumina and diazomethane⁵³ have been used to generate epoxides in 40-50% yield from selected steroidal ketones. Ring expanded products are also detected but in much lower yield than in the corresponding solution reaction.

Generation of Reactive Intermediates. Besides the dihalocarbenes already mentioned, other reactive intermediates have been generated on solid supports and isolated. Thus, α -diazocarbonyls, esters, and lactams have been conveniently prepared in 80-99% yield⁵⁴ by room temperature reaction of the corresponding mono-p-toluenesulfonylhydrazones with basic alumina. Simple aldehyde and ketone p-toluenesulfonylhydrazones do not decompose to diazoalkanes under these conditions. The reaction conditions are very mild and the method has found use in a number⁵⁵ of syntheses. Similarly, resonance stabilized phosphonium⁵⁶ and sulfonium⁵⁷ ylides can be generated in good yield by reacting the corresponding "onium" salt with basic alumina containing 1% potassium hydroxide at room temperature.

Miscellaneous Reactions. Room temperature reaction⁴² of Diels-Alder substrates whose solution cycloaddition normally require elevated temperatures has been accomplished in good yield on silica gel.

The Cab-O-Sil/bromine reagent previously mentioned has been utilized to add bromine to the double bond of diethyl fumarate to yield exclusively meso-diethyl-2,3-dibromosuccinate⁵⁸ at room temperature without additional catalyst.

The electrolytic lamellar reagent graphite bisulfate ($C_24HSO_4^+ \cdot 2H_2SO_4$) has been utilized with great success (< 90% yield) to achieve the room temperature esterification⁵⁹ of carboxylic acids with one equivalent of a variety of alcohols. The reagent serves the dual function of being an acid catalyst and a dehydrating reagent, the latter function by virtue of the hydrophillic graphite oxide generated as a by-product. Sulfuric acid alone or on an acid resin support can not begin to match the efficacy of the lamellar reagent.

Neutral alumina impregnated with 1-2% pyridine⁶⁰ has been shown to be an effective system for the dehydration of terpenoid alcohols at reflux temperature without significant isomerization of the olefins generated.

Finally, Chemical Abstracts lists literally hundreds of reagents deposited upon various supports by inorganic chemists who, more often than not, are unaware of their synthetic organic potential. An astute organic chemist might reap tremendous benefits by investigating such systems as metal cluster carbonyls of Ni, Mo, and Rh on silica gel or alumina⁶¹ and the enormous variety of transition⁶² metal salts (e.g. TiF_4) deposited on non-polymeric supports. These systems, and many more, have been fully

developed and characterized. Chemical Abstracts most frequently lists these potential reagent systems under the name of the support in the Compound Index.

Summary. A number of advantages can be associated in part or in whole with the use of solid supported reaction systems. Uniformly, they tend to be inexpensive, easy to generate, easy to work up, and frequently yield better results with greater selectivity and fewer side reactions under milder conditions than the corresponding solution reaction. The only extra expense associated with the reactions is with the support, which is usually quite inexpensive. Many of the reagent systems, especially those on graphite, are commercially available. Uniformly, the work-up is non-aqueous (i.e. not acidic or basic) and consists simply of filtration followed by rotary evaporation. The product isolated is usually pure due to the preferential and tenacious tendency of impurities to adsorb on the support. The concept of the use of the supports as diluents in dilution reactions is both intriguing and promising.

The amount of work that remains to be done in this area is enormous. A rationale for all of the advantages enumerated above is desirable. An investigation of the range and applicability of the systems, which currently often don't extend beyond the researcher's own interests, needs to be undertaken. The elucidation of heterogeneous mechanisms, function of the support and even the nature of the support-reagent system remains a formidable obstacle. Finally, and probably most importantly, the myriad of potential reagent systems already generated cry out for investigation.

BIBLIOGRAPHY

1. Akt.-Ges. Für Chemiewerte, Brit. 231, 901, April 5, 1924; Chem. Abstr., 19, 3571 (1925).
2. D. C. Neckers, J. Chem. Educ., 52, 695 (1975).
3. P. R. Rony and J. F. Roth in "Catalysis-Heterogeneous and Homogeneous," B. Delmon and G. Jannes, Ed., Elsevier Scientific Publishing Co., N.Y., N.Y., 1975, p. 373.
4. (a) R. K. Iler, "The Colloid Chemistry of Silica and Silicates," Cornell University Press, Ithaca, N.Y., 1955 ; (b) R. Calvert, "Diatomaceous Earth," The Chemical Catalog Co., Inc., N.Y., N.Y., 1930; (c) C. E. Marshall, "The Colloid Chemistry of the Silicate Minerals," Academic Press Inc., N.Y., N.Y., 1949; (d) B. G. Linsen, Ed., "Physical and Chemical Aspects of Adsorbents and Catalysts," Academic Press, N.Y., N.Y., 1970.
5. M. Fetizon and M. Golfier, C. R. Acad. Sci., Ser. C, 267, 300 (1968).
6. F. J. Kakis, M. Fetizon, N. Douchkine, M. Golfier, P. Mourgues, and T. Prang, J. Org. Chem., 39, 523 (1974).
7. M. Fetizon and P. Mourgues, Tetrahedron, 30, 327 (1974).
8. (a) M. Fetizon, M. Golfier, and J.-M. Louis, Chem. Commun., 1102 (1969); (b) J. Bastard, M. Fetizon, and J. C. Gramain, Tetrahedron, 29, 2867 (1973).
9. (a) M. Fetizon, M. Golfier, and J.-M. Louis, Chem. Commun., 1118 (1969); (b) M. Fetizon, M. Golfier, and J.-M. Louis, Tetrahedron, 31, 171 (1975).
10. M. Fetizon, F. Gomez-Parra, and J.-M. Louis, J. Heterocyclic Chem., 13, 525 (1976).
11. M. Fetizon, Y. Henry, N. Moreau, G. Moreau, M. Golfier, and T. Prang, Tetrahedron, 29, 1011 (1973).

12. (a) V. Balogh, M. Fetizon, and M. Golfier, *Angew. Chem. Internat. Edit.*, 8, 444 (1969); (b) T. Kametani, A. Kozuka, and K. Fukumoto, *J. Chem. Soc. (C)*, 1021 (1971); (c) V. Balogh, M. Fetizon, and M. Golfier, *J. Org. Chem.*, 36, 1339 (1971).
13. (a) J.-P. Laval and A. Verdier, *C.R. Acad. Sci., Ser. C*, 277, 425 (1973); (b) M. Fetizon, M. Golfier, R. Milcent, and I. Papadakis, *Tetrahedron*, 31, 165 (1975).
14. G. Büchi and H. Wüest, *J. Org. Chem.*, 36, 609 (1971).
15. (a) M. Fetizon, M. Golfier, and J.-M. Louis, *Tetrahedron Lett.*, 22, 1931 (1973); (b) M. Fetizon, M. Golfier, M. T. Montaufier, and J. Rens, *Tetrahedron*, 31, 987 (1975).
16. M. Fetizon, M. Golfier, and P. Mourgues, *Tetrahedron Lett.*, 43, 4445 (1972).
17. J.-M. Lalancette, G. Rollin, and P. Dumas, *Can. J. Chem.*, 50, 3058 (1972).
18. J. G. Hooley and M. Reimer, *Carbon*, 13, 401 (1975).
19. H. B. Kagan, *CHEMTECH*, 510 (1976).
20. (a) M. Hodler, H. Thommen, and H. Mayer, *Chimia*, 28, 723 (1974); (b) R. G. Riley and P. E. Kolattukudy, *Arch. Biochem. Biophys.*, 171, 276 (1975); (c) J. K. Seydel, K.-J. Schaper, E. Wempe, and H. P. Cordes, *J. Med. Chem.*, 19, 483 (1976); (d) R. G. Riley, R. M. Silverstein, J. A. Katzenellenbogen, and R. S. Lenox, *J. Org. Chem.*, 39, 1957 (1974).
21. (a) G. H. Posner, R. B. Perfetti, and A. W. Runquist, *Tetrahedron Lett.*, 39, 3499 (1976); (b) H.-L. Pan, C.-A. Cole, and T. L. Fletcher, *Synthesis*, 716 (1975).
22. F. A. Lamb, P. N. Cote, B. Slutsky, and B. M. Vittimberga, *J. Org. Chem.*, 39, 2796 (1974).
23. L. N. McCullagh and D. S. Wulfman, *Synthesis*, 422 (1972).
24. E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, 41, 260 (1976).
25. N. H. Andersen and H.-s. Uh, *Synthetic Commun.*, 3, 115 (1973).
26. (a) B. Franck, G. Dunklemann, and H. J. Lubs, *Angew. Chem. Inter. Ed.*, 6, 1075 (1967); (b) B. Franck and H. J. Lubs, *Liebigs Ann. Chem.*, 720, 131 (1968).
27. E. C. Taylor, C.-S. Chiang, A. McKillop, and J. F. White, *J. Am. Chem. Soc.*, 98, 6750 (1976).
28. M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," Vol. IV, John Wiley and Sons, N.Y., N.Y., 1974, pp. 492-497.
29. J.-M. Lalancette and R. Roussel, *Can. J. Chem.*, 54, 2110 (1976).
30. G. H. Posner and A. W. Runquist, *Tetrahedron Lett.*, 42, 3601 (1975).
31. A. Ichihara and T. Matsumoto, *Bull. Chem. Soc. Jap.*, 47, 1030 (1974).
32. (a) F. Hodosan and N. Serban, *Rev. Roumaine Chim.*, 14, 121 (1969); (b) F. Hodosan, N. Serban, and V. Ciurdu, *ibid.*, 14, 1303 (1969).
33. F. Hodosan and V. Ciurdu, *Tetrahedron Lett.*, 22, 1997 (1971).
34. G. P. Boldrini and A. Umani-Ronchi, *Synthesis*, 596 (1976).
35. (a) D. V. Ramana and C. N. Pillai, *Can. J. Chem.*, 47, 3705 (1969); (b) D. V. Ramana and C. N. Pillai, *Indian J. Chem.*, 8, 1106 (1970); (c) M. P. K. Unni, S. Santhanagopalan, and C. N. Pillai, *J. Indian Chem. Soc.*, 582 (1973).
36. V. Z. Sharf, L. Kh. Freidlin, E. N. German, and N. K. Vorob'eva, *Bull. Acad. Sci. of U.S.S.R., Chem. Ser.*, 8, 1768 (1970).
37. S. Malinowski, W. Kiewlicz, and E. Soltys, *Bull. Soc. Chim. Fr.*, 439 (1963).
38. F. Hodosan and I. Jude, *Rev. Roumaine Chim.*, 14, 1057 (1969).

39. F. Hodosan, I. Jude, and N. Serban, *Bull. Soc. Chim. Fr.*, 2691 (1964).
40. D. F. Kuemmel, *Chemistry and Industry*, 1882 (1966).
41. (a) T. Kameo and O. Manabe, *Chemistry Letters*, 33 (1972); (b) T. Kameo, S. Nishimura, and O. Manabe, *Nippon Kagaku Kaishi*, 1, 122 (1974); (c) T. Kameo and O. Manabe, *ibid.*, 1, 195 (1974).
42. M. Hudlicky, *J. Org. Chem.*, 39, 3460 (1974).
43. M. J. Rosen and J. Gandler, *J. Phys. Chem.*, 75, 887 (1971).
44. A. P. Lecuyer, J. L. Luche, H. B. Kagan, G. Colin, and C. Mazieres, *Bull. Soc. Cim. Fr.*, 1690 (1973).
45. J.-M. Lalancette and J. Lafontaine, *J. Chem. Soc., Chem. Commun.*, 815 (1973).
46. G. H. Posner, D. Z. Rogers, C. M. Kinzig, and C. M. Curria, *Tetrahedron Lett.*, 42, 3597 (1975).
47. J.-M. Lalancette, M.-J. Fournier-Breault, and R. Thiffault, *Can. J. Chem.*, 52, 589 (1974).
48. R. Baird and S. Winstein, *J. Am. Chem. Soc.*, 85, 567 (1963).
49. (a) Z. Cohen, E. Keinan, Y. Mazur, and T. H. Varkony, *J. Org. Chem.*, 40, 2141 (1975); (b) Z. Cohen, E. Keinan, Y. Mazur, and A. Ulman, *J. Org. Chem.*, 41, 2651 (1976); (c) E. Keinan and Y. Mazur, *Synthesis*, 523 (1976).
50. E. Proksch and A. de Meijere, *Angew. Chem.*, 88, 802 (1976).
51. (a) N. C. Deno, R. Fishbein, and C. Pierson, *J. Am. Chem. Soc.*, 92, 1451 (1970); (b) Ch. Eden and Z. Shaked, *Israel J. Chem.*, 13, 1 (1975).
52. F. Serratosa, *J. Chem. Educ.*, 41, 564 (1964).
53. P. A. Hart and R. A. Sandmann, *Tetrahedron Lett.*, 5, 305 (1969).
54. J. Muchowski, *Tetrahedron Lett.*, 16, 1773 (1966).
55. (a) J. Meinwald, J. C. Shelton, G. L. Buchanan, and A. Courtin, *J. Org. Chem.*, 33, 99 (1968); (b) G. Seitz and W. Klein, *Tetrahedron*, 29, 253 (1973).
56. (a) F. Serratosa, *J. Chem. Educ.*, 46, 302 (1969); (b) M. J. Berengeur, J. Castells, R. M. Galard, and M. Moreno-Manas, *Tetrahedron Lett.*, 6, 495 (1971).
57. J. Quintana, M. Torres, and F. Serratosa, *Tetrahedron*, 29, 2065 (1973).
58. M. J. Rosen and C. Eden, *J. Phys. Chem.*, 74, 2303 (1970).
59. J. Bertin, H. B. Kagan, J.-L. Luche, and R. Setton, *J. Am. Chem. Soc.*, 96, 8113 (1974).
60. E. von Rudloff, *Can. J. Chem.*, 39, 1860 (1961).
61. G. C. Smith, T. P. Chojnacki, S. R. Dasgupta, K. Iwatate, and K. L. Watters, *Inorg. Chem.*, 14, 1419 (1975).
62. E. Buscarlet, P. Touzain, M. Armand, and L. Bonnetain, *C. R. Acad. Sci., Ser. C*, 280, 1313 (1975).

THIOPHILIC ADDITION OF ORGANOMETALLIC REAGENTS TO THIOCARBONYLS

Reported by Sharon Fradenburgh

March 31, 1977

Grignard reagents and other organometallic compounds have been used for some time in the synthesis of substituted alcohols from carbonyl compounds by addition of the organic moiety to the carbonyl carbon. It might be expected that organometallics would react similarly with thiocarbonyl compounds. Of this class of compounds, thioketones have been the most widely studied, but others, such as dithioacids, dithioesters, trithiocarbonates, thioamides, thioacid chlorides, and β -thioketoesters, have also been examined. Contrary to expectations, many of these compounds add organometallics in the reverse sense so that the organic moiety is attached to sulfur, forming sulfides. Additional products which have been identified result from addition at carbon, double addition (*i.e.*, addition at both carbon and sulfur), reduction, enethiolization, alkylation of enethiols, dimerization, and formation of episulfides.¹⁻⁴ Some thiocarbonyls containing five-membered rings yield products with six-membered rings.^{1a} Allylic Grignards apparently can react at either end of the allylic "anion", giving linear or rearranged products.⁵ These reagents are also thought to form an intermediate which undergoes sigmatropic rearrangement to the final product.⁶⁻⁸ In all these reactions, product distribution depends a great deal on the structures of the reactants and on reaction conditions such as solvent and temperature.

Attempts to explain the addition of nucleophiles to the sulfur of thiocarbonyls have involved such approaches as polarity measurements, molecular orbital calculations,⁹ and the principle of hard and soft acids and bases (HSAB).¹⁰ A number of mechanisms have been proposed, including anionic or two-electron transfer, radical or one-electron transfer, carbenic intermediates, or initial addition at carbon followed by rearrangement.¹¹⁻¹⁸ Although the last alternative has been excluded in at least some cases,^{11a} there is insufficient evidence concerning the others. It has been suggested that a single mechanism does not seem to fit all the observations and that perhaps two or more competing pathways are available for the reactions.¹³ No complete study has been undertaken to date to determine the detailed mechanism.

Thiocarbonyls, because of their tendency to add carbanions at the sulfur, are potentially useful in synthesis as "umpolung", or inverted polarity, synthons for carbonyls, allowing formation of compounds with two functional groups in a dissonant relationship,¹⁹ *i.e.*, the polarity induced by one group at each atom in the molecule is opposite to that induced by the other group. Ketene dithioacetals, available from the reaction of Grignards and dithioesters, are also useful synthetic intermediates.^{7,20,21}

BIBLIOGRAPHY

- (a) D. Paquer and S. Smadja, *Recl. Trav. Chim. Pays-Bas*, **95**, 175 (1976); (b) D. Paquer and R. Pou, *Bull. Soc. Chim. Fr.*, 3887 (1972); (c) D. Paquer and J. Vialle, *C. R. Acad. Sc., Ser. C*, **275**, 589 (1972); (d) D. Paquer, *Bull. Soc. Chim. Fr.*, 1439 (1975); (e) D. Paquer and J. Vialle, *ibid.*, 3327 (1969).
- (a) M. Dagonneau, P. Metzner, and J. Vialle, *Tetrahedron Lett.*, 3675 (1973); (b) M. Dagonneau, D. Paquer, and J. Vialle, *Bull. Soc. Chim.*

- Fr., 1699 (1973); (c) P. Metzner and J. Vialle, *ibid.*, 1703 (1973); (d) M. Dagonneau, C. R. Acad. Sc., Ser. C, 279, 285 (1974).
3. L. Leger and M. Saquet, C. R. Acad. Sc., Ser. C, 279, 695 (1974).
 4. F. C. V. Larsson and S. O. Lawesson, Recl. Trav. Chim. Pays-Bas, 94, 1 (1975).
 5. F. Barbot and P. Miginiac, Tetrahedron Lett., 3829 (1975).
 6. V. Rautenstrauch, Helv. Chim. Acta, 57, 496 (1974).
 7. L. Leger, M. Saquet, A. Thuillier, and S. Julia, J. Organomet. Chem., 96, 313 (1975).
 8. (a) L. Morin and D. Paquer, C. R. Acad. Sc., Ser. C, 282, 353 (1976); (b) L. Morin, D. Paquer, and S. Smadja, Recl. Trav. Chim. Pays-Bas, 95, 179 (1976).
 9. (a) A. Julg, M. Bonnet, and Y. Ozias, Theor. Chim. Acta, 17, 49 (1970); (b) S. Inagaki, H. Fujimoto, and K. Fukui, J. Am. Chem. Soc., 98, 4054 (1976).
 10. For a review of HSAB see R. G. Pearson, ed., "Hard and Soft Acids and Bases," Dowden, Hutchinson & Ross, Inc., Stroudsburg, Pennsylvania, 1973.
 11. (a) P. Beak and J. W. Worley, J. Am. Chem. Soc., 92, 4142 (1970); (b) P. Beak and J. W. Worley, *ibid.*, 94, 597 (1972).
 12. (a) M. Dagonneau, J. F. Hemidy, D. Cornet, and J. Vialle, Tetrahedron Lett., 3003 (1972); (b) M. Dagonneau and J. Vialle, Bull. Soc. Chim. Fr., 2067 (1972); (c) M. Dagonneau and J. Vialle, Tetrahedron Lett., 3017 (1973); (d) M. Dagonneau and J. Vialle, Tetrahedron, 30, 415 (1974); (e) M. Dagonneau and J. Vialle, *ibid.*, 30, 3119 (1974); (f) M. Dagonneau, J. Organomet. Chem., 80, 1 (1974).
 13. P. Beak, J. Yamamoto, and C. J. Upton, J. Org. Chem., 40, 3052 (1975).
 14. J. C. Scaiano and K. U. Ingold, J. Am. Chem. Soc., 98, 4727 (1976).
 15. L. Leger and M. Saquet, Bull. Soc. Chim. Fr., 657 (1975).
 16. A. Ohno, K. Nakamura, M. Uohama, S. Oka, T. Yamabe, and S. Nagata, Bull. Chem. Soc. Jpn., 48, 3718 (1975).
 17. (a) G. Levesque, G. Tabak, and F. Outurquin, C. R. Acad. Sc., Ser. C, 280, 1289 (1975); (b) G. Levesque, G. Tabak, F. Outurquin, and J. C. Gressier, Bull. Soc. Chim. Fr., 1156 (1976).
 18. V. I. Savin, Zh. Org. Khim., in translation, 12, 262 (1976).
 19. D. Evans, seminar at the University of Illinois, Sept. 14, 1976.
 20. J. C. Wesdorp, J. Meijer, P. Vermeer, H. J. T. Bos, L. Brandsma, and J. F. Arens, Recl. Trav. Chim. Pays-Bas, 93, 184 (1974).
 21. D. Seebach, B. T. Gröbel, A. K. Beck, M. Braun, and K. H. Geiss, Angew. Chem., Int. Ed. Engl., 11, 443 (1972).

SYNTHESES OF SUBSTITUTED IMIDAZO[4,5-g]QUINAZOLINES:

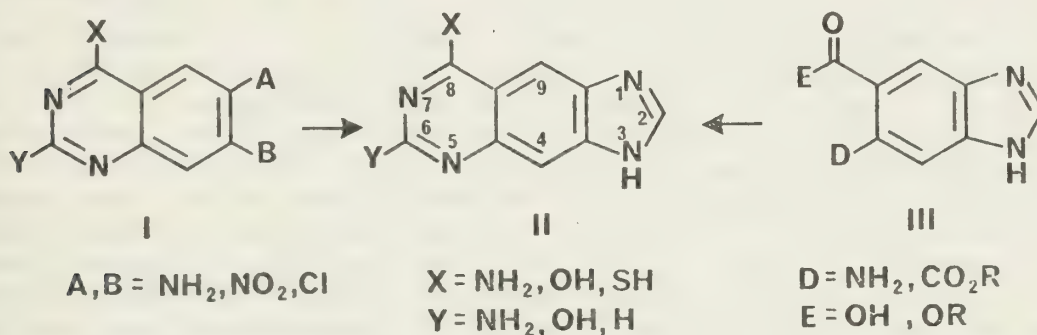
"STRETCHED" PURINES

Reported by Gene E. Keyser

April 4, 1977

Analogues of purine bases, nucleosides, and nucleotides have shown great utility¹ in the pharmaceutical industry and in the study of the naturally occurring compounds. Over the past fifteen years, N. J. Leonard and his group have been interested in modified base moieties used to study substrate-enzyme-coenzyme interactions. Most recently they have undertaken the syntheses²⁻⁶ of substituted imidazo[4,5-g]quinazolines (II) or

Scheme I



lin-benzopurines, whose fluorescence properties have been a useful tool in the investigations. There are two basic approaches to the ring system as shown in Scheme I,^{2,5} although the degree and the nature of substitution on the bicyclic precursors varies greatly. This presentation discusses the advantages and disadvantages of several approaches from the experimental point of view, with regard to the ultimate substitution pattern.⁵

A major problem in the synthesis of these compounds and their precursors is their poor solubility in common solvents; proposal of any synthetic route must take this into account as a limiting factor. Additionally, the syzygial relationship of these compounds with purines necessitates the unequivocal establishment of their substitution patterns. To this end, UV models and NMR in conjunction with ¹⁵N labelling have been used,⁷ although alternate synthetic routes have lessened the burden on these methods.

Penultimate to the further usefulness of these analogues is the attachment of a β-D-ribose to position 3. Ribosidation of the 8-methylthio derivative followed by displacement of the methylthio group with ammonia produced lin-benzoadenosine,⁴ but related sequences have failed to yield the guanosine analogue. The ribosidation of ring system precursors and attempts to convert them to the guanosine analogue are discussed.

BIBLIOGRAPHY

1. (a) For example, see R. K. Robins, J. Med. Chem., 7, 186 (1964); (b) R. K. Robins, Heterocyclic Compounds, 8, 162 (1967); (c) J. A. Montgomery, T. P. Johnson, and Y. F. Sheely in "Medicinal Chemistry," Part 1, 3rd ed., A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970; (d) D. Cole, Univ. of Ill. Seminar Abstracts, Dec. 14, 1972.

2. N. J. Leonard, A. Morrice, and M. Sprecker, J. Org. Chem., 40, 356 (1975).
3. N. J. Leonard, A. Morrice, and M. Sprecker, ibid., 40, 363 (1975).
4. N. J. Leonard, M. Sprecker, and A. Morrice, J. Am. Chem. Soc., 98, 3987 (1976).
5. G. E. Keyser and N. J. Leonard, J. Org. Chem., 41, 3529 (1976).
6. D. I. C. Scopes, J. R. Barrio, and N. J. Leonard, Science, 195, 296 (1977).
7. D. Wiemer, D. I. C. Scopes, and N. J. Leonard, J. Org. Chem., 41, 3051 (1976).

GENERAL SYNTHESSES AND NEW APPLICATIONS OF POLYMERIC REAGENTS

Reported by Asokkumar Pal

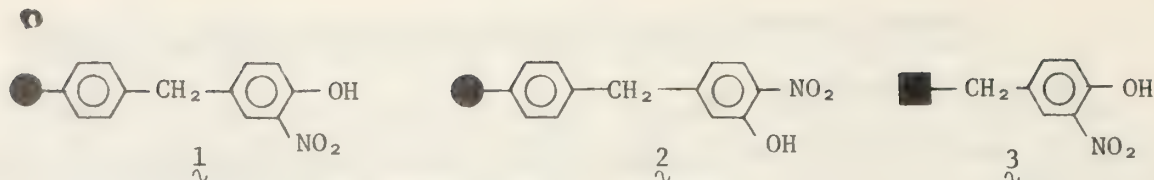
April 11, 1977

Historically, ion exchange resins can be considered as the earliest examples of polymeric reagents.¹ Two groups simultaneously emphasized the advantages of polymeric supports in organic syntheses.² Since then, polymeric reagents have been used to facilitate the syntheses of polypeptides,³ polynucleotides,⁴ and polysaccharides,⁵ to enhance the activity of catalysts,⁶ and to immobilize homogeneous catalysts⁷ and enzymes.⁸ Polymeric reagents have also been used in photosensitization,^{9,7d} in affinity chromatography,¹⁰ and in triphase catalysis.¹¹ In recent years insoluble polymers have been used in general organic synthesis of "non-repetitive, nonsequential" type, unlike the synthesis of polypeptides. Polymers are used as the carriers of low molecular weight reagents. The reagent moieties can be attached to a polymer covalently (most common), by interionic attraction or by complexation. "Polymeric reagents," thus defined, in general possess the physical characteristics of the polymer supports, while still possessing the chemical properties of the non-supported reagents. Mechanisms of reactions, except in isolated cases, remain essentially the same. Depending on the particular case, the reaction product is either obtained in solution or remains attached to the polymer (and is then cleaved off in a separate step). In two short reviews, Patchornik and Kraus¹² (1975), and Leznoff¹³ (1974) have discussed polymeric reagents used in various acylations,¹⁴ in Wittig reactions,¹⁵ in various condensations, in halogenations, in various cyclizations,¹⁶ in reductions, and in oxidations.¹⁷ We shall concentrate our report on several recently published polymeric reagents and their uses. Also included are several novel applications of polymeric reagents, and a review of the general methods of developing reagent moieties on polymeric supports, usually poly(styrene-0-2%-divinylbenzene) copolymer. In short, this report will be rather supplementary to earlier reviews.^{12,13}

The general sequence of reactions is as follows: (a) functionalization of the polymer, (b) attaching or developing the reagent moiety at the functionalized site, (c) reaction of a substrate (in solution) with the polymeric reagent, (d) physical separation of the product, and (e) finally, the regeneration of polymeric reagent, if possible. The step (a) is rather general and will be briefly discussed here, while other steps, specific to reagent moieties being attached or developed, will be individually discussed.

Functionalization

In almost all cases, a copolymer of styrene (or functionalized styrene) and 0-2% divinylbenzene (DVB) is used - the degree of rigidity of the resin is controlled by the amount of crosslinking agent DVB. In other cases, polyamides (Nylon 66), anion exchange resins (quarternary ammonium chlorides) (Section 2) and polyvinylpyridine¹⁸ were used. Except in rare cases, functionalization is always at the para-position of the phenyl ring^{19c}; multiple functionalization at meta- and/or ortho-positions (in addition to para-position) of the same ring rarely occurs (except in direct lithiation) and is undesirable. In one case,^{19a,b} polymeric reagent $\underset{\sim}{2}$ gave a poorer yield and less pure product than reagent $\underset{\sim}{1}$. We shall use a solid circle (●) to represent the polyethylene chain and all unfunctionalized phenyl rings when we need to show m- or o-substituents on the p-functionalized ring, while in most cases, since the functionalization is always at the p-position, a solid square in \blacksquare -X will represent the chain including the functionalized ring (-X being at the p-position), thus reagents $\underset{\sim}{1}$ and $\underset{\sim}{3}$ are identical.



When a functionalized monomer is used in polymerization, its proportion in the batch with styrene and DVB determines the concentration (milliequivalents per gram resin) of the functionalized group in the polymeric reagent. In some cases pure monomers are used in polymerization. Styrene with or without functionalized styrene and DVB is usually "emulsion" polymerized²⁰ and the polymer must be thoroughly cleaned²¹ (by washing it with 1N HCl, 1N NaOH, and then organic solvents) before initial functionalization or further modification of existing groups. This is particularly true with a solvent-swelling cross-linked polystyrene bead as it is more sensitive to surface impurities than a highly cross-linked macroreticular resin, since the latter contains pores of well-defined size and accessibility. However, washed solvent-swelling resins are usually more reactive and often give better yields than the macroreticular resins.²² Before functionalization of pre-formed polymer, the purity of the starting polymer must be ascertained,²¹ as minute amounts of surface impurities from the emulsifying agents, such as hydrated colloidal alumina or sodium lauryl sulfate, may prevent introduction of certain types of functional groups. The degree of functionalization, performed by several successive reactions depends on the first functionalization reaction; thus, the design of the process should be such that it yields reactive polymers with easily replaceable functional groups. Common "initial" functionalization reactions of polystyrene resins are given in Table 1.

Table 1. Functionalization of Poly(styrene-1-2%DVB): $\blacksquare\text{-H} \longrightarrow \blacksquare\text{-X}$

Process	Group X	Reaction	Ref.
(a) Bromination	-Br	(a) $\text{Ti}(\text{OAc})_3 \cdot 1.5\text{H}_2\text{O}$, Br_2 , CCl_4 . (b) FeCl_3 , Br_2 , CCl_4 , dark	23e 25a
(b) Aminomethylation	-CH ₂ NH ₂	(a) 1. $\text{CF}_3\text{CONHCH}_2\text{OH}$; 2. KOH-EtOH	23a
		(b) (X=Cl, Br), NH_2NH_2 , $\text{TFA-CH}_2\text{Cl}_2$	23a
		(c) 1. $\text{ClCH}_2\text{OCH}_3$; 2. K-phthalimide, DMF, 100° 5 hr; 3. $\text{NH}_2\text{NH}_2\text{-EtOH}$	23a
(c) Chloromethylation	-CH ₂ Cl	$\text{CH}_3\text{OCH}_2\text{Cl}$, BF_3	23b-d
(d) Lithiation	-Li	(a) 1. Bromination; 2. BuLi excess	26a
		(b) BuLi-TMEDA	26b
(e) Chlorosulfonation	-SO ₂ Cl	ClSO_3H , 70°, 30 min. then reflux in CCl_4	23f
(f) Arylation/Alkylation	-Ar,	(a) Cl-Ar , AlCl_3	19a
	-CH ₂ Ar	(b) $\text{ClCH}_2\text{OCH}_3$, then ArH, AlCl_3	
(g) Acylation	-COR(Ar)	ClCOR(Ar) , AlCl_3 , CCl_4	23g

The chloromethylation and bromination-lithiation processes for functionalization are most important (Tables 2, 3, and 4). The bromination method of Heitz *et al.*^{25a} (FeCl_3 , Br_2 , CCl_4) is often not reproducible^{23e} and brominated resin lacks homogeneity.^{25b} The method of Camps *et al.*^{23e} ($\text{Ti}(\text{OAc})_3$ •

1.5H₂O, Br₂ CCl₄) has the disadvantages that a large amount of costly thallium salt has to be used and a considerable washing is needed to remove the sparingly soluble thallic salt formed. However, Weinshenker *et al.*^{25c} using the latter method obtained bromination even to the extent of 4 meq/g. Lithiation is done by two methods: Braun's method^{26a} uses excess of BuLi on poly(p-halostyrene), halogen=Br, I; Chalk's method^{26b} involves direct lithiation with 1:1 complex of BuLi and N,N,N',N'-tetramethylethylenediamine (TMEDA). However, Evans^{26c} showed that the latter reaction led to *m*- and *p*-lithiation in 2:1 ratio. The bromination-lithiation route seems to be most suitable, -Br being completely replaced by -Li in one step with BuLi; also, multiple lithiation in the same phenyl ring is avoided. A comparison²⁴ of bromination-lithiation vs. direct lithiation (BuLi-TMEDA) indicates that the former is the method of choice, since predictable results can be obtained in bromination over a broad range of functionalization. Since the resin is swollen during bromination, a more even distribution of functional group can be achieved. Further derivatizations of ■-Br (Table 2), of ■-Li, obtained from 1% DVB crosslinked ■-Br with excess BuLi in PhH (Table 3),²⁴ and of ■-CH₂Cl (Table 4) lead to a variety of reagent moieties.

Table 2. ■-Br → ■-X

Reagent	Final Gr.
NaP(Ph) ₂	-P(Ph) ₂
BuLi	-Li

Table 3. ■-Li → ■-X

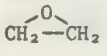


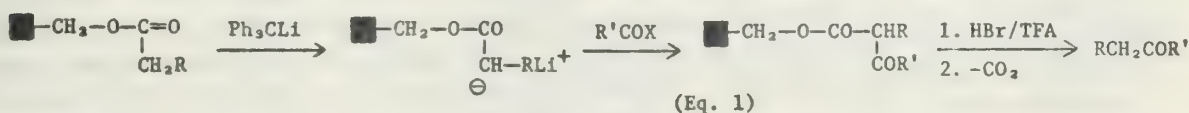
Reagent	Final Gr.	%
CO ₂	-COOH	90
S ₈	-SH	-
MeSSMe	-SMe	72
B(OMe) ₃	-B(OH) ₂	97
PhN=C=O	-CONHPh	80
SiMe ₂ Cl ₂	-SiMe ₂ Cl	65
ClP(Ph) ₂	-P(Ph) ₂	84
Me ₂ NCHO	-CHO	70
	-CH ₂ CH ₂ OH	85
PhCOPh	-C(Ph) ₂ OH	54
MgBr ₂ ·Et ₂ O	-MgBr	-

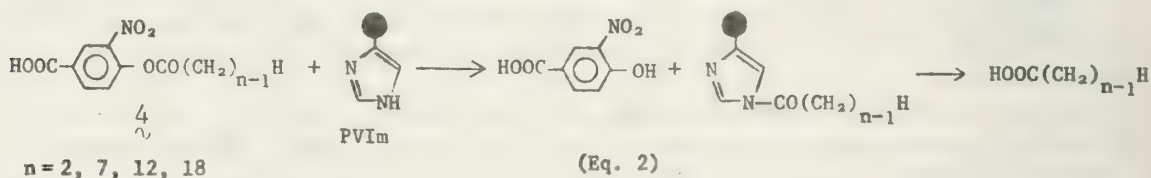
Table 4. ■-CH₂Cl → ■-CH₂X

Reagent	Final Gr.
 , AlCl ₃	-CH ₂ - 
K-phthalimide, DMF, NH ₂ NH ₂ , EtOH	-CH ₂ NH ₂
LiPPh ₂	-CH ₂ P(Ph) ₂
CH ₃ O-PPh ₂	-CH ₂ -P(Ph) ₂ O
DMSO	-CHO

The main advantages of a polymeric reagent over the monomeric counterpart in solution lie in the ease and selectivity of separation of products. Attachment of the reagent on polymer creates a microenvironment different from that of the reagent in solution. Crowley and Rapoport²⁷ have critically evaluated various aspects of solid phase syntheses, including polymer-supported catalysis. (a) The high dilution principle, that the reagent molecules on polymer are virtually so far apart that a condition of infinite dilution exists, has been supported by the observation of H-bonded and non-H-bonded carboxyl peaks in IR spectra of poly(styrene-2%-DVB)²⁸ with pendant -COOH groups (a free -COOH peak at 5.79 μm), by higher yield in mixed ester Dieckmann cyclization,¹⁶ cyclic peptide syntheses^{28b,c} and by successful acylation^{14a} and alkylation^{23e,28d} of active methylene esters bound to polymeric supports. The following reaction sequence provided a single ketone.^{23e}

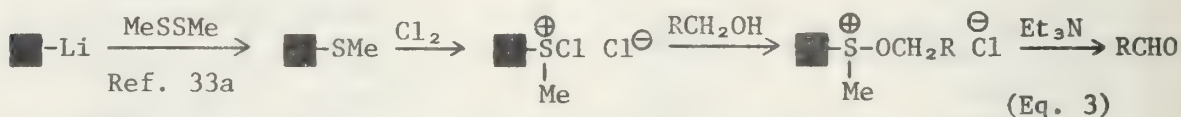


(b) On the other hand, when functional groups are closely held, a system of extremely high concentration prevails and forced combination^{14a} of moieties connected to the same macromolecule (intrapolymeric reaction²⁹) occurs. (c) Cooperative effects between two functional groups juxtaposed in an exact predetermined steric relationship afford enzyme-like properties.⁴⁴ (d) The microenvironment around the reagent molecule may offer some selectivity, e.g. in asymmetric (catalytic) hydrogenation³⁰ of olefins. In aqueous solution, apolar bonding between two hydrophobic molecules has been shown to increase the rate of hydrolysis of ester by polymer catalysts³¹ (Eq. 2). Hydrolysis of **4** ($n=12$) with synthetic, macroreticular catalyst polyvinylimidazole, PVI_m, was ca. 10^3 times as fast as with monomeric imidazole. The hydrolysis rates depended on the chain length of acyloxy group in **4** and on the solvent composition; the bulk of the rate enhancement was attributed to the apolar association of catalyst and substrate. (e) The microenvironment has been shown to change the distribution of reaction products.⁴²



Recently Reported Polymeric Reagents

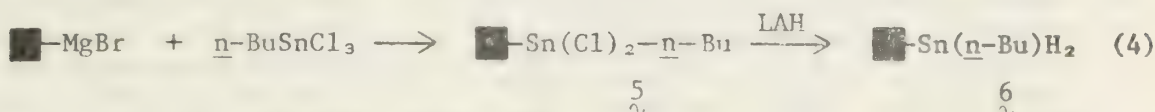
Section 1: Polymeric Thioanisole.^{25c} A polymeric sulfur-based oxidation method has the advantages of mildness of conditions, low cost, elimination of noxious odors, and avoidance of the difficulty of removing thioanisole from many products. Using the reagent $\text{■}-\text{SMeCl}^+\text{Cl}^-$ in oxidation of alcohols, the yields achieved were comparable to those with monomeric sulfur-based reagents.^{33b,c}



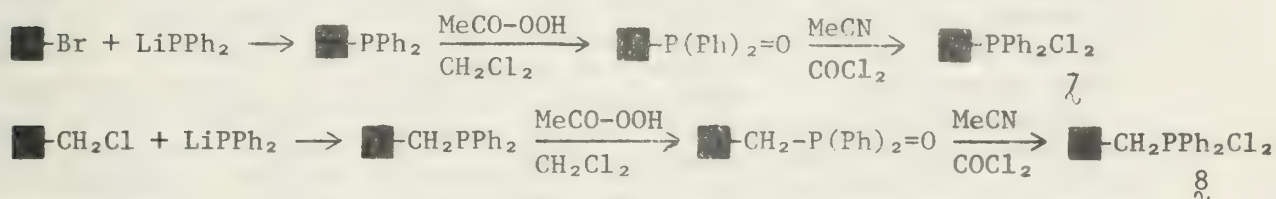
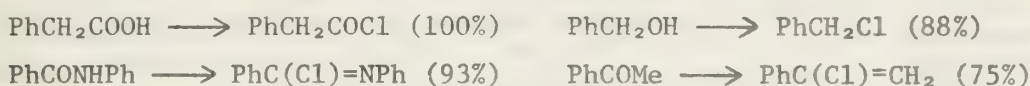
Section 2: Chromic Acid on Anion-Exchange Resin. Cainelli *et al.*³⁵ prepared an anion exchange resin containing CrO_4H^- (3.8 meq/g) by mixing the chloride form of Amberlyst A26 with an aqueous solution of CrO_3 , washing with acetone and ether, and drying under vacuum. High yields in oxidation of alcohols to aldehydes or ketones (86-98%) were achieved by refluxing the alcohol with excess resin. The nature of the solvent does not affect the yield and the method is quite general for allylic, benzylic or saturated primary and secondary alcohols. No traces of carboxylic acids were noted in the oxidation products.

Section 3: Polymeric Organotin Reagent. The versatility and selectivity of organotin hydrides as reducing agents are well established.³⁷ Weinshenker *et al.*^{25b} have developed a polymeric tin hydride reagent, **6**, which has all the advantages of tin hydride reagent as well as those of polymeric reagents; also the reagent avoids the malodors and toxic vapors characteristic of tin hydrides.^{37b} The reagent can be easily stored, preferably as **5**, in cold, and is easily regenerated with $\text{LiAlH}_4/\text{THF}$. Examples of yield in reductions with reagent **6** include PhCOMe (92%), $t\text{-BuCOMe}$ (91%), and $n\text{-heptanal}$ (86%). In reduction of alkyl and aryl halides in the presence of other functional groups, reagent **6** is superior to LAH or more recently introduced methods.^{37c} Yields over 90% are often achieved. In reductions

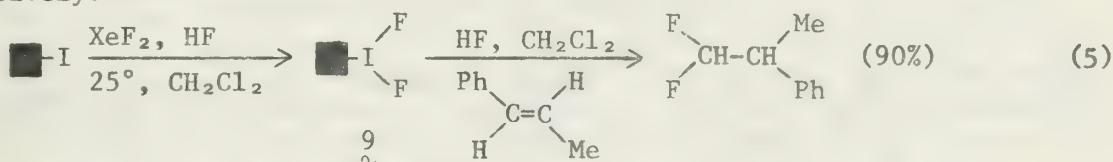
of *n*-octyl bromide to *n*-octane and of benzyl bromide to toluene, the respective yields were 94% and 98%.



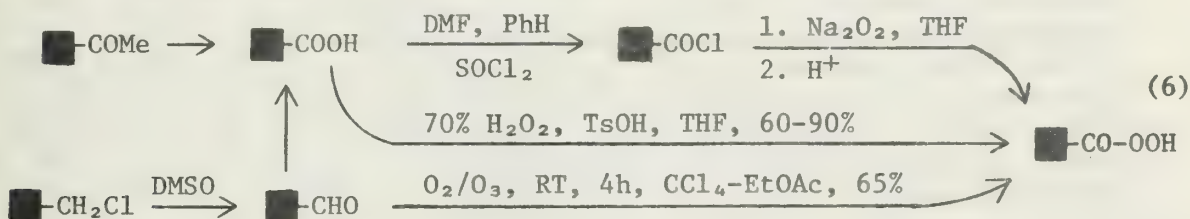
Section 4: Polymer-supported Trisubstituted Phosphine Dichloride Reagent.²¹ The reagents 7 and 8 behave like mild forms of PCl_5 .³⁸ The reagents have been employed for the preparation of acid chlorides from acids, imidoyl chlorides from anilides, nitriles from primary amides, alkyl chlorides from alcohols, and chloroolefins from ketones, usually by refluxing with the starting compound in CH_2Cl_2 or MeCN. Yields are often quite high. A few examples are given below:



Section 5: Fluorination of Olefins to Gem-difluorides.^{39a} Aryliodine (III) difluorides have been used to fluorinate 1,1-diphenylethene (CHCl_3 , -25° , 63%)^{39b} and styrene^{39c} (CH_2Cl_2 , 0° , 2h, 37%). With the equivalent polymeric reagent, 9, the respective yields were improved to 96% and 86% respectively.^{39a}



Section 6: Polymeric Reagent with Perbenzoic Acid Moieties. Polymeric^{40a} peroxides were made as early as 1964; the product was a copolymer containing sulfonic as well as carboxylic acid residues, and could be used only in aqueous solvents. Recently Frechet *et al.*^{40b-d} have made polymeric resins containing perbenzoic acid units which can be used in any solvent. It is quite stable, can be dried and stored in the cold for a long time and can be regenerated easily. Good yields were achieved in epoxidation of olefins. The major factors affecting yields are the swelling properties of the solvent and the degree of cross-linking.

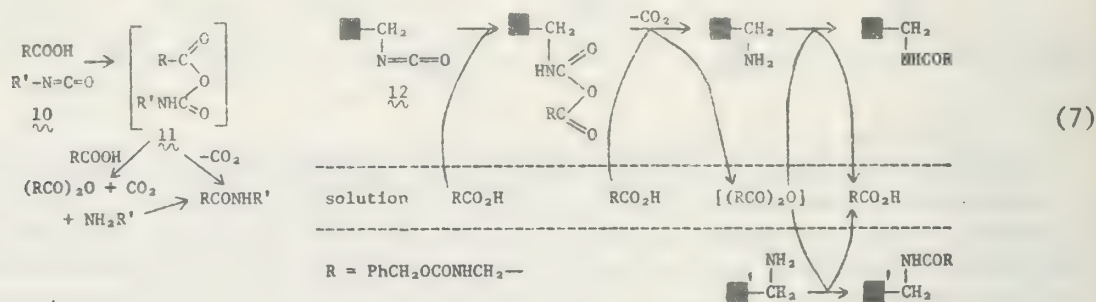


Recently several other reagents have been reported. Selenium containing reagents³² have been made from poly(*p*-aminostyrene): poly(*p*-selenocyanatostyrene), poly(*p*-hydroselenostyrene), poly(phenylselenostyrene),

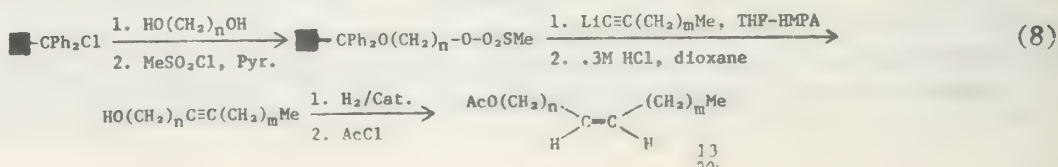
and poly(p-phenylseleninylstyrene). No synthetic use of these reagents has been reported. N-Chlorinated polyamide^{34a}, prepared^{34b} from Nylon 66, has been used to oxidize alcohols (1° and 2°) and sulfides. The reagent poly(4-vinylpyridine), P4VP, is treated with NaBH₄ in water, when a solid³⁶ (P4VP-BH₃) separates; P4VP-BH₃ reduces aldehydes and ketones in dry boiling PhH. Roush⁴¹ made a polymeric tosyl azide reagent, $\text{---SO}_2\text{N}_3$, which was indefinitely stable at room temperature, and never detonated on shock treatment. These reagents do not increase yields appreciably (compared with conventional monomeric reagents), but offer other advantages of polymeric reagents, like the ease of separation and an enhanced purity of product.

Novel Applications of Polymeric Reagents

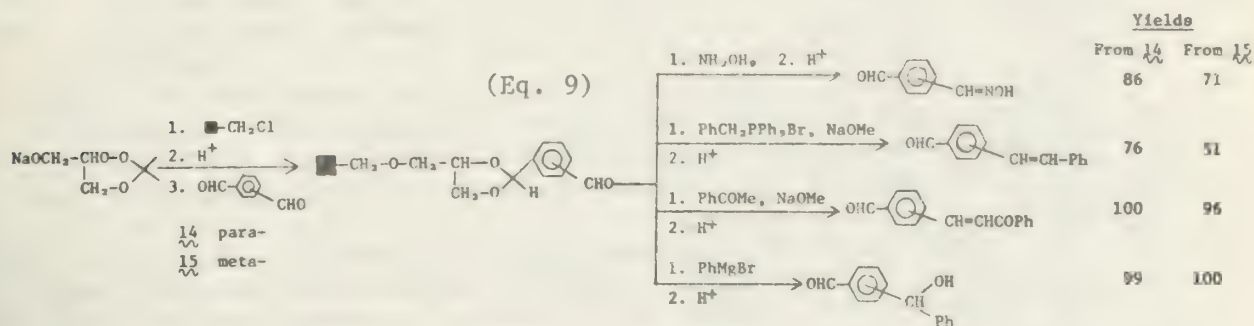
Application 1: The Three Phase Test For Reactive Intermediates.^{45a-f}
A precursor for a suspected intermediate can be attached to one polymeric support and the intermediate may be liberated by reaction with an appropriate reagent in solution and trapped in the presence of a second polymeric reagent bearing the trapping agent; the detection of an adduct gives a positive evidence for a free intermediate. Rebek *et al.* applied this principle in the detection of cyclobutadiene intermediates,^{45a,e} of nucleophilic catalysis intermediates,^{45b} of elimination reaction intermediates,^{45b} of acylation reaction intermediates,^{45f} and of metaphosphate intermediates in various phosphorus transfer reactions.^{45c,d} In the reaction of acids with isocyanates, the product could arise from 11 by intramolecular rearrangement or by disproportionation to the symmetrical anhydride. When polymer-bound isocyanate 12 was treated with $\text{PhCH}_2\text{OCONHCH}_2\text{COOH}$ in pyridine, acylation occurred readily to give polymer-bound glycine derivative. However, when the reaction was performed in the presence of a second polymer-bound reagent, $\text{---CH}_2\text{NH}_2$, 80% of acylation was done on the latter polymer suggesting that the symmetrical anhydride was the acylating agent.



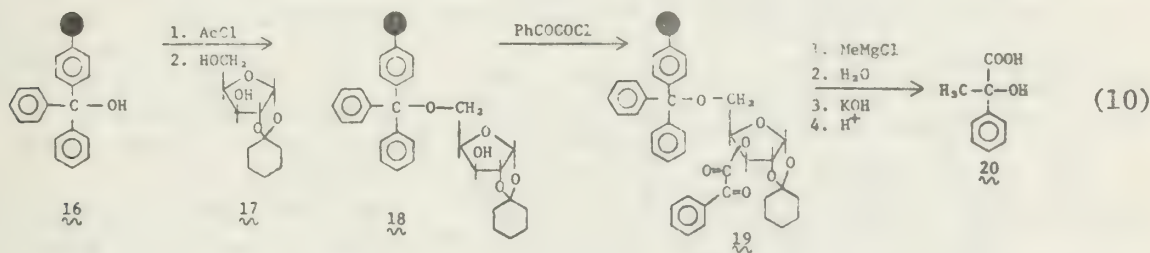
Application 2: Monoreaction On Symmetrical Bifunctional Compounds.
Chemical reaction of 1 mole of bifunctional compound with 1 mole of reagent in solution invariably leads to a mixture of unreacted compound, mono-, and bi-reacted products. Ideally, if a diol molecule can be attached to an insoluble polymer chain, chemical modification can be easily done on the free -OH group and later the product can be cleaved off to give the free mono-alcohol which can be further modified in a different way. Exactly this has been achieved: monoacetate^{46b} and monotrityl ether^{46a} have been made from a diol. An application of the same principle was made in synthesizing^{46d} the insect sex attractants^{46c} of the general formula 13 (Eq. 8).



Similarly one -CHO group in a dialdehyde can be attached to a polymer thru an acetal linkage, and further reaction at the free -CHO group can be done (Eq. 9).^{46e} This method made possible synthesis of several unreported compounds. 15 consistently gave less yield than 14, suggesting an influence of steric factors on the m-CHO group. One disadvantage of acetal protection is that only basic conditions can be applied.



Application 3: Asymmetric Synthesis of Atrolactic Acid. Kawana et al.⁴³ first reported asymmetric synthesis on an insoluble polymeric support (Eq. 10).



Poly(styrene-2% DVB) was treated with PhCOCl and AlCl₃ in CS₂ to give 20% benzoylated polymer which gave reagent 16 quantitatively on reaction with PhMgCl in THF. The chlorination of 16 with acetyl chloride followed by the treatment with 17 in PhH-pyridine gave 18 (80% conversion). Reaction of 18 with phenylglyoxyl chloride resulted in 19 which was subjected to asymmetric Grignard reaction followed by hydrolysis and acidification to give the acid 20 in 77% chemical and 65% optical yields.

Summary

The advantages of using polymers as reagents and carriers in organic syntheses have been discussed. On the whole, the polymeric reagents will become attractive to the future chemist due to their numerous advantages and due to the availability of chemical means for developing a variety of reagent moieties on the polymeric materials.

BIBLIOGRAPHY

1. K. Dorfner, "Ion-Exchange: Properties and Applications," Ann Arbor Science Publication, Michigan, 1972.
2. (a) R. B. Merrifield, J. Am. Chem. Soc., 85, 2149 (1963); (b) R. L. Letsinger and M. J. Kornet, *ibid.*, 85, 3045 (1963).
3. (a) M. A. Barton, R. U. Lemieux, and J. Y. Savoie, *ibid.*, 95, 4501 (1973); (b) D. Yamashiro and C. H. Li, *ibid.*, 95, 1310 (1973); (c) G. R. Marshall and R. B. Merrifield, "Biochemical Aspects of Reactions on Solid Supports," Academic Press, New York, 1971.
4. (a) R. L. Letsinger and V. Mahadevan, J. Am. Chem. Soc., 88, 5319 (1966); (b) H. Koster, Tetrahedron Lett., 1527 (1972); (c) H. Seliger and G. Aumann, *ibid.*, 2911 (1973).
5. (a) J. M. Frechet and C. Schuerch, J. Am. Chem. Soc., 93, 492 (1971);

- (b) M. Kawana and S. Emoto, *Bull. Chem. Soc. Japan*, 46, 160 (1974).
6. (a) R. H. Grubbs and L. C. Kroll, *J. Am. Chem. Soc.*, 93, 3062 (1971);
(b) Report of the "Organic Reactions Catalytic Society," Boston, April, 1975; (c) C. O. Evans, *J. Org. Metal. Chem.*, 7, 296 (1974).
7. (a) J. C. Bailer, Jr., *Cat. Rev. Sci. Eng.*, 10, 17 (1974); (b) Z. M. Michalska and D. E. Webster, *Platinum Metals Review*, 18, 65 (1974);
(c) C. U. Pittman, Jr. and L. R. Smith, *J. Am. Chem. Soc.*, 97, 1749 (1975); (d) C. U. Pittman, Jr. and R. M. Hanes, *ibid.*, 98, 5402 (1976);
(e) C. U. Pittman, Jr. and G. O. Evans, *Chem. Tech.*, 560 (1973).
8. (a) O. Zabrosky, "Immobilized Enzymes," CRC Press, Cleveland, 1973;
(b) *Chem. and Eng. News*, Aug. 18, p 22 (1975); (c) K. Mosbach, "Enzymes Bound to Artificial Matrices," *Sci. Amer.*, 224, 26 (1971);
(d) L. B. Wingard, ed., "Enzyme Engineering," John Wiley, New York, 1972.
9. (a) C. Manning and C. C. Leznoff, *Can. J. Chem.*, 53, 805 (1975); (b) J. Y. Wong, C. Manning, C. C. Leznoff, *Angew. Chem. Int. Ed. Engl.*, 13, 666 (1974); (c) Y. Kansoka and Y. Migita, *Tetrahedron Lett.*, 3693 (1976);
(d) B. Sket and M. Zupan, *Synth. Commun.*, 6, 309 (1976); (e) A. P. Schaap, A. L. Thayer, E. C. Blossey, and D. C. Neckers, *J. Am. Chem. Soc.*, 97, 3741 (1975).
10. (a) E. Seymour and J. M. Frechet, *Tetrahedron Lett.*, 3669 (1976); (b) J. M. Frechet and G. Pelle, *J. Chem. Soc. Chem. Commun.*, 225 (1975);
(c) J. M. Frechet and E. Seymour, *Tetrahedron Lett.*, 1149 (1976).
11. (a) S. L. Regen, *J. Am. Chem. Soc.*, 97, 5956 (1975); (b) S. L. Regen and L. Dulak, *ibid.*, 99, 623 (1977) and references therein.
12. A. Patchornik and M. A. Kraus, *Pure Appl. Chem.*, 43, 503 (1975).
13. C. C. Leznoff, *Chem. Soc. Rev.*, 3, 65 (1974).
14. (a) A. Patchornik and M. A. Kraus, *J. Am. Chem. Soc.*, 92, 7587 (1970);
(b) T. Lien and H. J. Harwood, *J. Macromol. Sci., Chem.*, A7, 1079 (1973);
(c) M. H. Karger and Y. Mazur, *J. Am. Chem. Soc.*, 90, 3878 (1968); (d) M. B. Shambhu and G. A. Digenis, *Tetrahedron Lett.*, 1627 (1973).
15. (a) F. Camps, J. Castells, J. Font, and F. Vela, *Tetrahedron Lett.*, 1715 (1971); (b) S. V. McKinley and J. W. Rakshys, Jr., *J. Chem. Soc., Chem. Commun.*, 134 (1972); (c) W. Heitz and R. Michels, *Angew. Chem. Int. Ed. Engl.*, 11, 298 (1972).
16. (a) J. I. Crowley and H. Rapoport, *J. Am. Chem. Soc.*, 92, 6363 (1970);
(b) A. Patchornik and M. A. Kraus, *ibid.*, 92, 7587 (1970).
17. (a) N. M. Weinshenker and C.-M. Shen, *Tetrahedron Lett.*, 3281 (1972);
(b) N. M. Weinshenker and C.-M. Shen, *Tetrahedron Lett.*, 3285 (1972).
18. (a) D. C. Neckers, D. A. Kooistra, and G. W. Green, *J. Am. Chem. Soc.*, 94, 9284 (1972); (b) E. C. Blossey, L. M. Turner, and D. C. Neckers, *Tetrahedron Lett.*, 1823 (1973).
19. (a) R. Kalir, M. Fridkin, and A. Patchornik, *Europ. J. Biochem.*, 42, 151 (1974); (b) G. T. Panse and D. A. Laufer, *Tetrahedron Lett.*, 4181 (1970); (c) E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, 3, 338 (1970).
20. (a) S. R. Sandler, "Polymer Syntheses," Academic Press, New York, 1974;
(b) A. D. Jenkins, "Polymer Science," American Elsevier Pub. Co., New York, 1972.
21. H. M. Relles and R. W. Schluez, *J. Am. Chem. Soc.*, 96, 6469 (1974).
22. (a) J. M. Frechet and L. J. Nuyens, *Can. J. Chem.*, 54, 926 (1976); (b) J. M. Frechet and K. E. Haque, *Macromolecules*, 8, 130 (1975).
23. (a) A. R. Mitchel, S. B. H. Kent, B. W. Erickson, and R. B. Merrifield, *Tetrahedron Lett.*, 3795 (1976); (b) R. B. Merrifield, *J. Am. Chem. Soc.*, 85, 2149 (1963); (c) K. W. Pepper, H. M. Paisley, and M. A. Young, *J. Chem. Soc.*, 4097 (1953); (d) R. B. Merrifield, *Biochem.*, 3, 1385 (1964);
(e) F. Camps, J. Castells, M. J. Ferrando, and J. Font, *Tetrahedron Lett.*, 1713 (1971); (f) M. Rubinstein and A. Patchornik, *ibid.*, 2881 (1972); (g) M. Kawana and S. Emoto, *ibid.*, 4855 (1972).
24. M. J. Farrall and J. M. Frechet, *J. Org. Chem.*, 41, 3877 (1976).

25. (a) W. Heitz and R. Michels, *Makromol. Chem.*, 148, 9 (1971); (b) N. M. Weinshenker, G. A. Crosby, and J. Y. Wong, *J. Org. Chem.*, 40, 1966 (1974); (c) C. U. Crosby, N. M. Weinshenker, and H.-S. Uh, *J. Am. Chem. Soc.*, 97, 2232 (1975).
26. (a) D. Braun, *Makromol. Chem.*, 30, 85 (1959); (b) A. J. Chalk, *J. Polym. Sci., Part B*, 6, 649 (1968); (c) D. C. Evans, L. Phillips, J. A. Barrie, and M. H. George, *J. Polym. Sci., Polym. Chem. Ed.*, 12, 147 (1974).
27. J. I. Crowley and H. Rapoport, *Acc. Chem. Res.*, 9, 135 (1976).
28. (a) R. L. Letsinger, M. J. Kornet, V. Mahadevan, and D. M. Jerina, *J. Am. Chem. Soc.*, 86, 5163 (1964); (b) M. Fridkin, A. Patchornik, and E. Katchalski, *ibid.*, 87, 4646 (1965); (c) M. Fridkin, A. Patchornik, and E. Katchalski, *ibid.*, 88, 3164 (1966); (d) M. A. Kraus and A. Patchornik, *Isr. J. Chem.*, 9, 269 (1971).
29. C. G. Overberger and K. N. Sannes, *Angew. Chem. Int. Ed. Engl.*, 13, 99 (1974).
30. (a) R. H. Grubbs and L. C. Kroll, *J. Am. Chem. Soc.*, 93, 3062 (1971); (b) N. Takaishi, H. Imai, C. A. Bertelo, and J. K. Stille, *ibid.*, 98, 5400 (1976).
31. C. G. Overberger and J. C. Salamone, *Macromolecules*, 2, 553 (1969).
32. (a) M. Kato, R. Michels, and W. Heitz, *J. Polym. Sci., Polym. Lett.*, 14, 413 (1976).
33. (a) F. G. Bordwell, B. M. Pitt, *J. Am. Chem. Soc.*, 77, 572 (1955); (b) E. J. Corey and C. U. Kim, *ibid.*, 94, 7586 (1972); (c) E. J. Corey and C. U. Kim, *J. Org. Chem.*, 38, 1233 (1973).
34. (a) H. Schuttenberg, G. Klump, U. Kaczmar, S. R. Turner, and R. C. Schulz, *J. Macromol. Sci., Chem.*, A7, 1085 (1973); (b) H. Schuttenberg and R. C. Schulz, *Makromol. Chem.*, 143, 153 (1971).
35. G. Cainelli, G. Cardillo, M. Orena, and S. Sindri, *JACS*, 98, 6738 (1976).
36. (a) M. L. Hallensleben, *J. Polym. Sci., Symposium*, 47, 1 (1974); (b) R. P. Baenes, J. H. Graham, and M. D. Taylor, *J. Org. Chem.*, 23, 1561 (1958).
37. (a) R. J. Ingham, S. D. Rosenberd, and H. Gilman, *Chem. Rev.*, 60, 459 (1960); (b) H. G. Kuivilla, *Synthesis*, 10, 499 (1970); (c) T. L. Ho and C. M. Wong, *Synth. Commun.*, 3, 237 (1973); *J. Org. Chem.*, 31, 2688 (1966).
38. G. A. Wiley, R. L. Hershkowitz, and B. M. Rein, *J. Am. Chem. Soc.*, 86, 964 (1964).
39. (a) M. Zupan, A. Pollak, *J. Chem. Soc. Chem. Commun.*, 715 (1975); (b) J. Bornstein, M. R. Borden, F. Nunes, and H. I. Tarlin, *J. Am. Chem. Soc.*, 85, 1609 (1963); (c) W. Carpenter, *J. Org. Chem.*, 31, 2688 (1966).
40. (a) F. Helfferich, and D. B. Luten, Jr., *J. Appl. Polym. Sci.*, 8, 2899 (1964); (b) J. M. Frechet and K. E. Haque, *Macromolecules*, 8, 130 (1975); (c) C. R. Harrison and P. Hodge, *J. Chem. Soc. Perkin I*, 605 (1976); (d) *J. Chem. Soc. Chem. Commun.*, 1009 (1974).
41. W. R. Roush, D. Feitler, and J. Rebek, *Tetrahedron Lett.*, 1391 (1974).
42. C. Yaroslowsky and E. Katchalski, *Tetrahedron Lett.*, 3629 (1970), 5173 (1972).
43. M. Kawana and S. Emoto, *ibid.*, 4855 (1972).
44. G. Wulff, A. Sarhan, and K. Zabrocki, *ibid.*, 4329 (1973).
45. (a) J. Rebek and F. Gavina, *J. Am. Chem. Soc.*, 96, 7112 (1974); (b) J. Rebek, D. Brown, and S. Zimmerman, *ibid.*, 97, 454 (1975); (c) J. Rebek and F. Gavina, *ibid.*, 97, 1591 (1975); (d) J. Rebek and F. Gavina, *ibid.*, 97, 3221 (1975); (e) J. Rebek and F. Gavina, *ibid.*, 97, 3453 (1975); (f) J. Rebek, D. Brown, and S. Zimmerman, *ibid.*, 97, 4407 (1975).
46. (a) J. Y. Wong and C. C. Leznoff, *Can. J. Chem.*, 51, 2452 (1973); (b) T. M. Fyles and C. C. Leznoff, *Can. J. Chem.*, 54, 935 (1976); (c) D. A. Evans and C. L. Green, *Chem. Soc. Rev.*, 2, 75 (1973); (d) C. C. Leznoff and T. M. Fyles, *J. Chem. Soc. Chem. Commun.*, 251 (1976); (e) C. C. Leznoff and J. Y. Wong, *Can. J. Chem.*, 51, 3756 (1973).

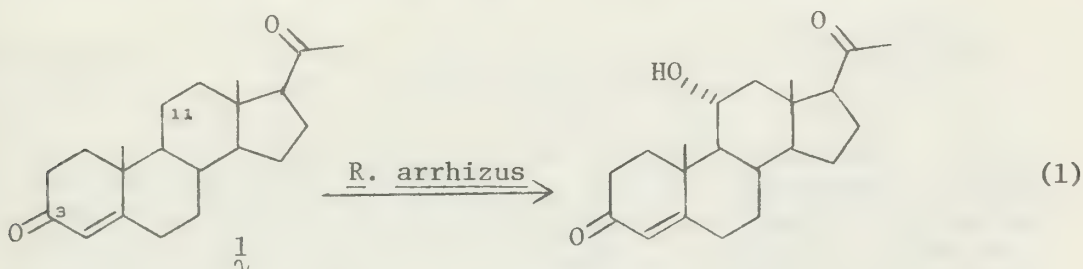
MICROORGANISMS IN ORGANIC CHEMISTRY: HYDROXYLATIONS AT
UNACTIVATED C-H BONDS OF NATURAL PRODUCTS

Reported by Keith Allan Dregler

April 18, 1977

Introduction. The regio-specific reactions of organic chemistry are chemically associated with the presence of functional groups. Usually there is a requirement for bond polarization through the presence of a good leaving group or adjacent activating groups. Substitutions at centers that are not endowed with such advantages are difficult using purely classical chemical means. A successful approach to this problem in steroid chemistry¹ has been the use of microorganisms for the hydroxylations of unactivated C-H bonds. This seminar will examine the synthetically useful microbiological hydroxylations that have been developed since 1970 for the formation of analogs of steroids, alkaloids, and terpenes which would be difficult to get through purely chemical means.

Steroids. Due to the physiological properties of many steroids, their synthesis has presented many challenges to the organic chemist. Particularly challenging is the introduction of functional groups at remote sites, a process which generally requires many tedious steps chemically. In 1952, Peterson and Murray² reported that progesterone (1) is hydroxylated at the 11 α -position by the fungus Rhizopus arrhizus in 20% yield (Eq. 1).

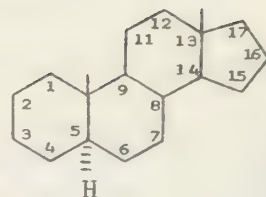


This work opened the way for the quick and simple production of pharmacologically important cortical hormones. It also led to an almost ceaseless deluge of research into the hydroxylations of steroids with many, many organisms during the 1950's and 1960's. There are several books available cataloging known reactions through the late 1960's,^{1,3-7} and almost every position of the steroid nucleus has been hydroxylated.

Most of the previous hydroxylations were performed on steroids possessing a 3-keto- Δ^4 system.¹ It was felt that this system probably had a great directing influence which possibly masked other useful reactions.⁸ In order to get a more fundamental understanding of the scope and synthetic utility of steroidal hydroxylations, a British group⁸⁻²⁷ under the direction of Sir Ewart R. H. Jones has undertaken an extensive study of microbiological hydroxylations of steroids which lack the 3-keto- Δ^4 system.

It was hoped that by varying the position of the oxygen substituent around the steroid nucleus, different patterns of hydroxylated products could be obtained in sufficient yields to warrant the use of microorganisms as a useful means of obtaining desired analogs. The first set of substrates used by Jones were mono-oxygenated 5 α -androstanes^{9,10,11} with a few known hydroxylating fungi,¹ Rhizopus nigricans, Colonectria decora, and Aspergillus ochraceus. Most of the products obtained were dihydroxylated which would preclude the synthetic utility. However, this study points out

some potentially useful aspects. The desire to direct hydroxylations to different positions of the steroid nucleus by merely changing the position of the original substituent was clearly achieved. Models revealed that the two oxygens introduced were always 3.8-4.5 Å apart and that distances from attacked carbon atom(s) to the site of the original oxygen substituent were also fairly constant. Substantial conversion to products occurred only when the substituent was in the A or D ring. These results were explained by postulating a model⁹ in which the enzyme possesses three sites, each one capable of binding and hydroxylating. Comparison of the products obtained from the hydroxylation of 5α-androstan-3-one (2) and 5α-androstan-17-one (3) by *C. decora* illustrates the model (See Figure 1).



5α-androstane

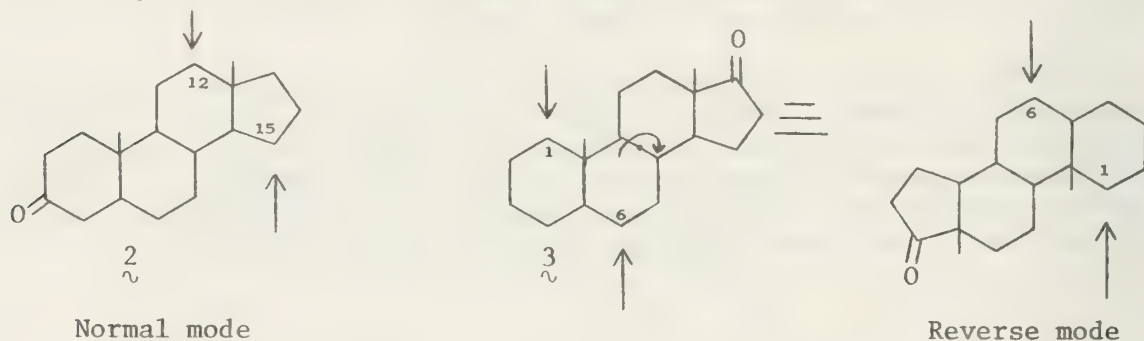


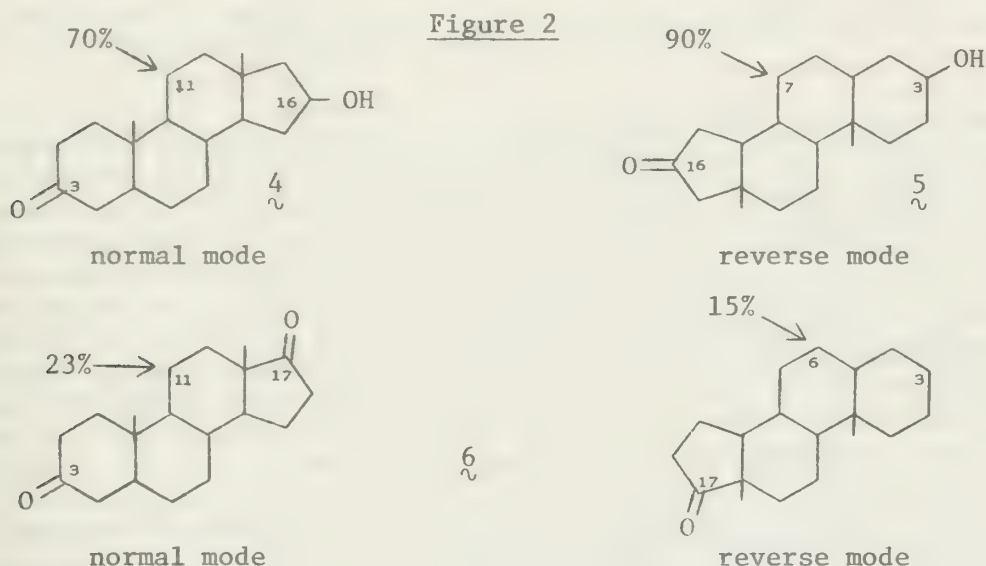
Figure 1

The 3-ketone (2) binds to the enzyme as shown and is hydroxylated at positions 12 and 15. This is designated "normal mode" binding. If the 17-ketone (3) is rotated 180° about an axis through the C 8-9 bond, the binding and hydroxylation pattern appears very similar to that in 2. This is classified as "reverse mode" binding. Binding in normal and reverse mode can also account for the 3α,11α- and 3β,7β- dihydroxy products of 5α-androstan-17-one obtained with *R. nigricans*.

The above results indicate that by choosing the position of the substrate's oxygen functions and microorganism used, different products can be obtained in a somewhat predictable fashion. Low yield and poor utilization of substrate hamper the synthetic utility. Jones^{10,12,13} then examined various dioxygenated 5α-androstanes. The presence of two oxygen functions could possibly facilitate the utility of the reactions by (1) increasing the polarity of the substrate and thus its solubility and ability to permeate cell walls and (2) directing the placement of the introduced hydroxyl group by varying the positions of the substituents.

These substrates were all much more highly utilized, yields generally higher, and monohydroxylations predominated. Consideration of the three sites involved in these reactions (the two original oxygen substituents and the carbon atom attacked) reveals the rough geometric relationships found previously with dihydroxylations.^{9,11} The three site enzyme model fits the results nicely. Since there are two polar sites to bind, the substrate would tend to line itself up inside the enzyme in such a way as to maximize the hydrophilic interactions at two of the sites. Hydroxylation occurs at the carbon(s) which come closest to the third. The yield and range of products would be determined by the precision of the fit in the enzyme. The symmetrical nature of the molecule would again lead to two possible binding modes. Some illustrations are given in Figure 2. Notice that (1) A ring

carbonyls with a D ring hydroxyl group (4) bind in a normal mode; (2) D ring carbonyls with an A ring hydroxyl group (5) bind in a reverse mode; and (3) A and D ring dicarbonyls (6) can bind in both modes. The results might suggest that A ring carbonyls exert a greater directing influence over the nature of the reaction and that the site at the "lower left" of the enzyme is the predominant binding site.



These results confirm that indeed one can direct, with some degree of predictability, the position of the hydroxylation by varying the positions of the oxygen substituents and the microorganism used. The oxidation level of the substituent can also be a very important characteristic in directing substitution as shown by the 11 α -hydroxylation of 16 β -hydroxy-5 α -androstan-3-one in 98% yield and the 7 α -hydroxylation of 3 β -hydroxy-5 α -androstan-16-one in 90% overall yield. A similar pattern was found with *Diaporthe celastrina*¹⁴ which converted 5 α -androstan-3,7-dione into its 3 β ,16 α -dihydroxy derivative (45%) while the 3 β -hydroxy-5 α -androstan-17-one was hydroxylated at the 9 α -position (55%) and 5 α -androstan-7,17-dione was transformed to the 3 α -hydroxy derivative (52%). It is interesting to note that *R. nigricans* had been extensively used for 11 α -hydroxylations in the past,¹ but through careful choice and design of substrate, substitution can be directed toward other sites very efficiently. *C. decora* is also synthetically useful for 1 β -hydroxylations of readily available 6,17- and 7,17-diketones.

Constant 11-hydroxylation was found with *A. ochraceus*¹⁰ which rules out the above enzyme model. Instead it appears to possess a site specific hydroxylating enzyme which is unaffected by the nature of the substrates.

The previous success in unmasking useful reactions of microorganisms prompted the extension of the work into investigating other fungi^{14,17} in hopes of revealing new efficient conversions which were otherwise hidden and unknown. *Rhizopus circinnas* was found to be useful for introducing a hydroxyl group into the 4 α -position of 5 α -androstan-11,17-dione in 54% yield.¹⁴ The 2 α -hydroxylation of steroids by microorganisms is a fairly rare reaction;¹ however, *Wojnowicia graminis* was found to perform this reaction (64% yield) on 5 α -androstan-7,17-dione.¹⁵ *Ophiobolus herpotrichus* will introduce an oxygen at the 16-position of 5 α -androstan-3,11-dione in 59% yield.¹⁵ The latter two fungi were also found to be efficient 17-hydroxylators of substrates oxygenated in the A and B rings. The fungus

Syncephalastrum racemosum¹⁶ was found to hydroxylate 3 β -hydroxy-5 α -androstan-7-one at the 12 α -position in 51% yield. Most of the results obtained with the above microorganisms could again be explained with the three site enzyme model and the two binding models. All of the above examples are of synthetic utility for making desired steroid analogs in sufficient quantity for chemical and biochemical study.

Previous studies had illustrated the importance of the oxidation level of the substrates in determining the position of substitution.^{12-14,16} Other studies were therefore conducted to evaluate the effects of various derivatives of ketones and alcohols (mainly acetals, thioacetals, and methoxy) on substitution patterns.^{18,19} Results were generally poorer with the derivative than the parent compound with a few useful exceptions. Daedalea rufescens,¹⁸ a previously unknown hydroxylator,¹ was found to convert 5 α -androstan-3,7-dione to the 3 β ,7 α ,16 β -trihydroxy product in 30% yield. Reduction of the 3-oxo group could be prevented by converting it into the acetal which also increased the yield to 66%. After hydrolysis, the 3-oxo-7 α ,16 β -dihydroxy product could be efficiently converted into 7 α ,16 β -dihydroxy-5 α -androstane in good yields by Huang-Minlon reduction. C. decora was found to convert 16,16-ethylenedioxy-5 α -androstane into its 6 α ,12 β -dihydroxy product in 71% yield.¹⁹ This represents one of the few efficient conversions of a monooxygenated substrate.

The synthesis of specific poly-oxygenated halogen containing steroids can also be challenging. Jones²⁰ looked at mono-halo, mono-oxygenated steroids as potentially useful substrates, since the halogen atom might present a competing directing influence leading to efficient conversions to the desired compounds. However, the only efficient conversion noted was the 1 β ,6 α -dihydroxylation of 3 α -fluoro, 3 α -chloro, and 3 α -bromo-5 α -androstan-17-one in yields of 41%, 70%, and 65% respectively using C. decora. With A. ochraceus, 3-fluoro-5 α -androstan-17-one was converted to the 11 α -hydroxy compound in 73% yield. This fluorinated androstane was chemically converted to 3-fluoro-5 α -androstan-11,17-dione, which was a new compound.

Due to the physiological activity of pregnanes, dioxygenated derivatives might be useful substrates.²¹ Due to the conformational mobility of the C-17 acetyl group, it was thought that the substrate would be able to maximize binding interaction leading to clean and efficient hydroxylations. However, yields tended to be less than those with the corresponding 5 α -androstanes. Therefore, the synthesis of a specific hydroxylated pregnane would be best accomplished by hydroxylation of the appropriate oxygenated 5 α -androstan-17-one and introduction of the side chain chemically.

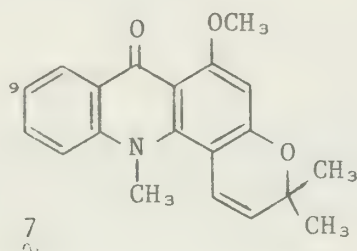
These studies have shown that careful construction of the substrate, paying particular attention to the position and oxidation level of the oxygenated substituents, and choice of the microorganism used can lead to directed functionalizations of unactivated C-H bonds. Some of these recent discoveries have been used in conjunction with chemical means for synthesizing desired substituted ring systems. Some examples are presented.

The chemical preparation of 1-oxo-5 α -steroids from 3-ketones requires the trans A/B ring junction for enolization toward the 2-position,²² and therefore is not useful for preparing similar 5 β -steroids. A microbiological route has been described²³ in which incubation of 5 α -androstan-6,17-dione with C. decora gives the 1 β -hydroxy compound in 56% yield. This compound was equilibrated to its cis ring junction followed by Huang-Minlon reduction of the 6 and 17-ketones to yield 5 β -androstan-1-ol.

For the studies on mono-oxygenated 5 α -androstan-3-one, ^{9,11} it was necessary to have 15-oxygenated 5 α -androstan-3-one. Chemical conversions of Δ^{14} - and Δ^{15} -17-ketones were long and not suited to obtaining gram quantities.²⁴ An efficient route to the desired compound was developed using microorganisms at various stages.²⁵ Hydroxylation of 3-hydroxy-5 α -androstan-17-one by *A. ochraceus* gave the 11 α -hydroxy derivative. Chemical removal of the 17-keto group followed by oxidation gave the 3,11-dione. This was hydroxylated in the 15-position by *Penicillium urticae* followed by removal of the 3- and 11-keto groups to give the desired compounds.

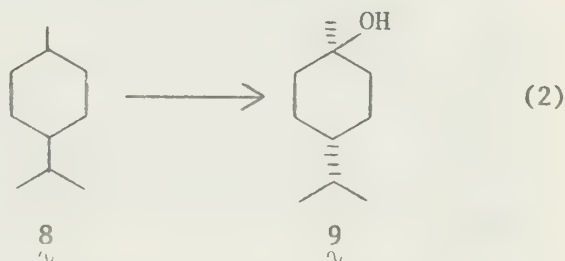
Routes to 3,7-, 3,11-, 3,12-, 7,11-, 7,17-, and 11,17-dioxygenated 5 α -androstan-3-one using microbiological hydroxylations as a critical step were also developed.²⁶ These were hard to prepare through chemical means.⁹ The sequences are too long to present in detail here, but through the use of 3 β -hydroxy-5 α -androstan-17-one, 17 β -hydroxy-5 α -androstan-3-one, and 5 α -androstan-3,17-dione (all commercially available), Jones was able to develop routes to all the desired compounds in satisfactory yields by taking advantage of the earlier findings¹³ that the use of substrates containing oxygen substituents at different oxidation levels yield different hydroxylation patterns.

Alkaloids. Microbiological hydroxylations of alkaloids has suffered from generally poor yields and lack of research.^{3,4} Another disadvantage is that many of the known reactions can be carried out more efficiently chemically. J. P. Rosazzo²⁷ has reported the successful, large-scale 9-hydroxylation of the antitumor alkaloid acronycine (7) in 30% yield using *Cunninghamella echinulata*.



Terpenes. Terpene microbiological hydroxylations have also suffered low yields and lack of extensive research.⁴ However, recent studies are finding much more success in developing microbiological routes to compounds difficult to obtain chemically.

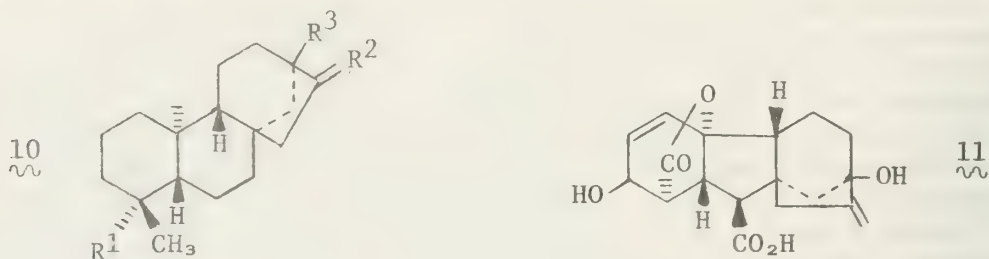
A Japanese group²⁸ has studied some reactions in connection with the formation of monoterpenoids useful for perfumes. One useful procedure to come out of this study is the synthesis of *cis*-p-menthan-1-ol (9) from p-menthane (8) with a strain of *Pseudomonas* in 20% yield (Eq. 2). Though the yield was low (the conditions had not been optimized), the reaction was completely stereospecific. This method is superior to chemical conversions from p-menthane in which six tertiary p-menthanols can be formed which would have to be separated.



Gibberellic acid, a C-19 norditerpene obtained from the fungus *Gibberella fujikuroi*, causes growth stimulation in higher plants.²⁹

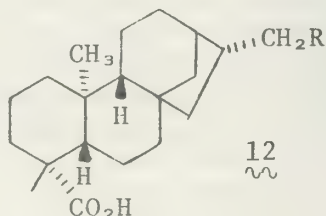
Because of its potential agricultural use, its biosynthesis and metabolism have been widely studied, necessitating the acquisition of some unusually oxygenated intermediates and analogs. This has resulted in a large amount of research being done to find microbiological routes to these compounds since chemical conversions would probably be very long and tedious.

The tetracyclic diterpene ent-kaurenoic acid (10; $R^1 = \text{CO}_2\text{H}$, $R^2 = \text{CH}_2$, $R^3 = \text{H}$) has been shown to be involved in gibberellic acid (11) biosynthesis.³⁰ Many studies have called for various oxygenated analogs



of ent-kaurenoic acid. These have been accomplished through the use of microorganisms and some of the results are presented below.

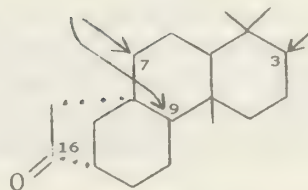
An Australian group³¹ conducted a study on the hydroxylations of various compounds possessing the ent-kaurene skeleton using A. ochraceus, C. decora, and R. nigricans. The latter two showed a predilection for introducing a hydroxy group at C-1 or C-7 in yields of 10-40%. The transformation of ent-kaurenoic acid into ent-7 β -hydroxykaurenoic acid in 25% yield by R. nigricans is particularly significant since the latter is a known biosynthetic intermediate to gibberellins.³² Another group was able to improve on this³³ by first converting the ent-kaurenoic acid to the β -hydroxypropionic acid derivative (10; $R^1 = \text{CO}_2(\text{CH}_2)_2\text{CO}_2\text{H}$, $R^2 = \text{CH}_2$). The derivative was then incubated with G. fujikuroi which gave, after saponification, a 38% yield of 7 β -hydroxykaurenoic acid. The hydroxyacid (12, $R = \text{OH}$) can be obtained in large quantities from Beyeria calycina.³⁴ It is hydroxylated in 20% yield at the 7 β -position by C. decora.³³ Conversion of the metabolite to the primary tosylate (12, $R = \text{OTs}$) followed by displacement by iodine (12, $R = \text{I}$) and dehydrohalogenation yields the hydroxylated kaurenoic acid. Even though the yield is lower than above, the starting material is readily and cheaply available.



Due to the findings in steroid hydroxylations that the presence of a carbonyl group can direct hydroxylations,^{9,11} studies were conducted on ent-17-norkauran-16-one (10, $R^1 = \text{CH}_3$, $R^2 = \text{O}$) by McCrindle and Anderson.^{35,36} Using A. niger³⁵ the 3 α -hydroxy product was obtained in good yields.³ With R. nigricans³⁶ and the same substrate, the 3 α ,7 α -dihydroxylated product was obtained in 15% yield. With 17-norkauran-16-one serving as the substrate, A. niger³⁵ gave the 3 α -hydroxy product and R. nigricans³⁶ yielded the 3 β ,7 β - and 3 β ,9 α -dihydroxy derivatives in 21% and 15% respectively. The results with R. nigricans can be rationalized through the same model used for steroid oxidations.^{11,13} (See Figure 3.) The molecule would interact with the enzyme in the reverse mode leading to substitution at C-3 and C-7. Substitution at C-9 would arise by rotation about an axis through C-16, C-3 by 45° which would put C-9 in a favorable position to be hydroxylated. The

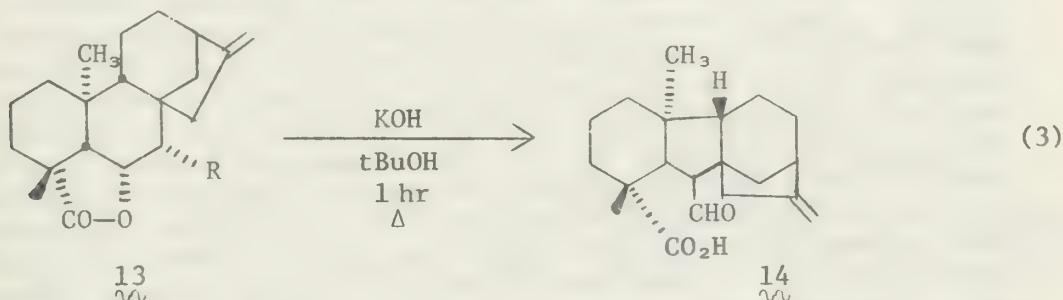
close similarities between this model and the steroid models might suggest a universal application to similar polycyclic substrates. However, more research in this area would be necessary.

Figure 3



The conversion of the above metabolites to their respective kaurene derivatives would simply require a Wittig reaction. However, the Wittig reaction may lead to base catalyzed isomerization products with highly oxygenated substrates.³⁷ Several alternative routes have been developed to get around this problem, one of which has already been mentioned.³³

Hanson³⁸ developed a route to specifically labelled [¹⁴C]-gibberellic acid which also avoids the problem with the Wittig reaction. The gibbane skeleton (14) can be formed from the rearrangement of the tosylate of 7 α -hydroxykaurenolide (13, R = OTs) with base.³⁷ (Eq. 3)



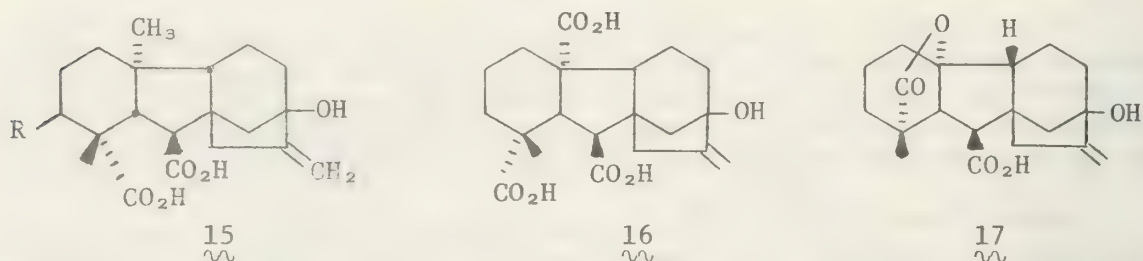
The aldehyde (14) was reduced to the alcohol and the exocyclic double bond converted to the ketone by ozonolysis. A Wittig reaction was used to re-introduce the ¹⁴C-methylene group and the product efficiently converted into [¹⁴C]-gibberellic acid by G. fujikuroi.

Another goal is the acquisition of diterpenes functionalized in the C-ring since these can potentially provide unusual functionalized gibberellins. Some satisfactory microbiological routes to the diterpenes and from the diterpene to the gibberellins have been developed. Hanson³⁹ found that *R. arrhizus* was able to convert *ent*-7 α -hydroxykaurenolide (13, R = H) into its 11 α - and 13 β -hydroxy derivatives in 10% and 20% respectively. These yields were satisfactory for sufficient conversion into gibberellins used for biological studies.

Steviol (10, R¹ = COOH, R² = CH₂, R³ = OH) is a C-ring functionalized diterpene which has been used as a substrate for preparing various gibberellins with G. fujikuroi.⁴⁰ There have been developed chemical methods for construction of the bicyclo[3,2,1] octane system with a bridge-head hydroxyl for the synthesis of steviol,⁴¹ but these are long and complicated sequences. Another route³¹ involves the hydroxylation of position 13- of *ent*-17-norkauren-16-one-19-oic acid (10, R¹ = CO₂H, R² = 0) by A. ochraceus in 5% yield which can be converted into steviol.^{41a} Though the yield is low, the recovered starting material can be recycled.

The use of various keto and hydroxy derivatives in steroidal work has met with limited success.^{18,19} An example in which a hydroxy derivative of a diterpene yielded a different and more useful product than the parent

compound is presented below. Steviol is metabolized into ent-7 α ,6 α ,13-trihydroxykaurenoic acid which is further transformed into GA₁ (15, R=H) and GA₁₆ (15, R=OH) by a mutant of G. fujikoroi.⁴² The C-13 acetate derivative of steviol (10, R³=OOCCH₃) blocks the 3 β -hydroxylation which provides a new preparative route to GA₁₇ (16) and GA₂₀ (17).⁴² The amount of steviol acetate derived from 5g of dried leaves of Stevia rebaudiana is converted by the G. fujikoroi mutant into the same quantity of GA₂₀ which can be isolated from 60kg of immature Pharbitis nil seeds.⁴³



Conclusion. Microorganisms are efficient agents for the selective oxidation of unactivated C-H bonds. They can quickly provide hydroxylated analogs of natural products for which chemical routes would be long and tedious. Current research on hydroxylations by microorganisms shows that the location of the introduced oxygen substituent can be directed to various positions of the steroid nucleus in a somewhat predictable manner. Continued research along these lines could make microorganisms a commonly used "reagent" for selective oxidations of natural products and possibly cyclic compounds in general (Jones has reported limited success with bicyclic ketones⁴⁴). Not only do microorganisms provide short, efficient paths, they perform the reaction without affecting other sensitive groups elsewhere in the molecule. This eliminates the need for elaborate protecting groups. Though research on the hydroxylation of nonsteroidal natural products is still generally plagued with low yields, progress is being made, and continued efforts should unveil new useful methods.

BIBLIOGRAPHY

1. W. Charney and H. L. Herzog, "Microbial Transformations of Steroids. A Handbook," Academic Press, New York, N.Y., 1967.
2. D. H. Peterson and H. C. Murray, J. Am. Chem. Soc., 74, 1871 (1952).
3. H. Iizuka and A. Naito, "Microbial Transformations of Steroids and Alkaloids," University Park Press, State College, Pa., 1967.
4. G. S. Fonken and R. A. Johnson, "Chemical Oxidations with Microorganisms," Marcel Dekker, New York, N.Y., 1972.
5. C. Vézina, S. N. Sehgal, K. Singh, and K. Kluepfel in "Progress in Industrial Microbiology," D. J. D. Hockenhull, ed., Churchill Livingstone, Edinburgh, London, 1971, Vol. 10, pp. 76-84.
6. D. H. Petterson, in "Biochemistry of Industrial Microorganisms," C. Rainbow and A. H. Rose, ed., Academic Press, New York, N.Y., 1963, pp. 538-558.
7. L. L. Smith, in "Terpenes and Steroids," K. H. Overton, ed., The Chemical Society, London, 1974, Vol. 4, pp. 394-453.
8. Sir E. R. H. Jones, Pure Appl. Chem., 33, 39 (1973).
9. A. M. Bell, P. C. Cherry, I. M. Clark, W. A. Denny, Sir E. R. H. Jones, G. D. Meakins, and P. D. Woodgate, J. Chem. Soc. Perkin I, 2081 (1972).
10. A. M. Bell, J. W. Browne, W. A. Denny, Sir E. R. H. Jones, A. Kasal, and G. D. Meakins, ibid., 2930 (1972).
11. J. W. Browne, W. A. Denny, Sir E. R. H. Jones, G. D. Meakins, Y. Morisawa, A. Pendlebury, and J. Pragnell, ibid., 1493 (1973).

12. A. M. Bell, W. A. Denny, Sir E. R. H. Jones, G. D. Meakins, and W. E. Müller, *ibid.*, 2759 (1972).
13. V. E. M. Chambers, W. A. Denny, J. M. Evans, Sir E. R. H. Jones, A. Kasal, G. D. Meakins, and J. Pragnell, *ibid.*, 1500 (1973).
14. A. M. Bell, A. D. Boul, Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, and A. L. Wilkins, *ibid.*, 1364 (1975).
15. A. M. Bell, I. M. Clark, W. A. Denny, Sir E. R. H. Jones, G. D. Meakins, W. E. Müller, and E. E. Richards, *ibid.*, 2131 (1973).
16. V. E. M. Chambers, Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, and A. L. Wilkins, *ibid.*, 55 (1975).
17. A. M. Bell, Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, and A. L. Wilkins, *ibid.*, 2040 (1975).
18. A. M. Bell, Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, and A. Pendlebury, *ibid.*, 357 (1975).
19. J. M. Evans, Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, A. Pendlebury, and A. L. Wilkins, *ibid.*, 1356 (1975).
20. Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, and A. L. Wilkins, *ibid.*, 2300 (1975).
21. Sir E. R. H. Jones, G. D. Meakins, J. O. Miners, R. N. Mirrington, and A. L. Wilkins, *ibid.*, 1842 (1976).
22. C. Djerassi, D. H. Williams, and B. Berkoy, *J. Org. Chem.*, 27, 2205 (1962).
23. J. E. Bridgeman, P. C. Cherry, Sir E. R. H. Jones, and G. D. Meakins, *Chem. Commun.*, 482 (1967).
24. C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Am. Chem. Soc.*, 87, 817 (1965).
25. J. W. Blunt, I. M. Clark, J. M. Evans, Sir E. R. H. Jones, G. D. Meakins, and J. T. Pinhey, *J. Chem. Soc. (C)*, 1136 (1971).
26. A. M. Bell, V. E. M. Chambers, Sir E. R. H. Jones, G. D. Meakins, W. E. Müller, and J. Pragnell, *J. Chem. Soc. Perkin I*, 312 (1974).
27. R. E. Betts, D. E. Walters, J. P. Rosazzo, *J. Med. Chem.*, 17, 599 (1974).
28. Y. Tsukamoto, S. Nonomura, and H. Sakai, *Agr. Biol. Chem. (Japan)*, 39, 617 (1975).
29. A. Lang, *Ann. Rev. Plant Physiol.*, 21, 537 (1970).
30. C. A. West, "The Biosynthesis of Bibberellins", in "Biosynthesis and its Control in Plants," B. V. Millborrow, ed., Academic Press, London, 1973.
31. J. P. Beily, E. L. Ghisalberti, P. R. Jefferies, M. A. Sefton, and P. N. Sheppard, *Tetrahedron Lett.*, 2589 (1973).
32. F. T. Lew and C. A. West, *Phytochemistry*, 10, 2065 (1971).
33. K. D. Kroft, E. L. Ghisalberti, P. R. Jefferies, T. R. Knox, T. J. Mahoney, and P. N. Sheppard, *Tetrahedron*, 30, 3663 (1974).
34. P. R. Jefferies and T. G. Payne, *Aust. J. Chem.*, 18, 1441 (1965).
35. (a) A. B. Anderson, R. McCrindle, and J. K. Turnbull, *Can. J. Chem.*, 53, 1182 (1975); (b) A. B. Anderson, R. McCrindle, J. K. Turnbull, *Chem. Commun.*, 143 (1973).
36. R. McCrindle, J. K. Turnbull, and A. B. Anderson, *J. Chem. Soc. Perkin I*, 1202 (1975).
37. D. C. Aldridge, J. R. Hanson, and T. P. C. Mulholland, *J. Chem. Soc.*, 3539 (1965).
38. J. R. Hanson and J. Hawker, *Phytochemistry*, 12, 1073 (1973).
39. J. R. Hanson, G. Savona, and M. Sivers, *J. Chem. Soc. Perkin I*, 2001 (1974).
40. J. R. Bearder, J. MacMillan, and C. M. Wels, *Chem. Commun.*, 778 (1973).
41. (a) I. F. Cook and J. R. Knox, *Tetrahedron Lett.*, 4091 (1970); (b) K. Mori, Y. Nakahara, and M. Matsui, *Tetrahedron*, 28, 3217 (1972).
42. J. R. Bearder, V. M. Frydman, P. Gaskin, J. MacMillan, C. M. Wels, and B. O. Phinney, *J. Chem. Soc. Perkin I*, 173 (1976).
43. N. Murofushi, N. Takahashi, T. Yokota, and S. Tamura, *Agric. Biol. Chem. (Japan)*, 32, 123 (1968).
44. A. S. Bailey, M. L. Gilpin, and Sir E. R. H. Jones, *J. Chem. Soc. Perkin I*, 265 (1977).

THE CHEMISTRY OF SELENIUM STABILIZED ALKYL CARBANIONS

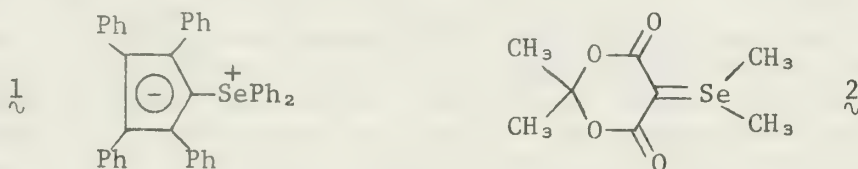
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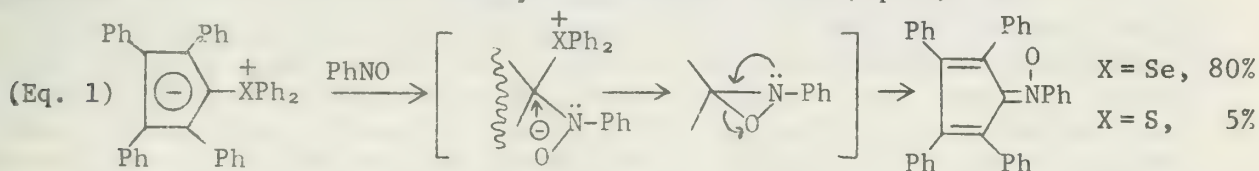
This seminar will deal with the preparation and utilization of carbanions which are stabilized to some extent by an adjacent selenium functionality. The properties of these compounds will be compared with their more familiar sulfur analogs in order to illustrate both the similarities and the unique features of selenyl carbanion chemistry.

Selenonium Ylides.¹ Several procedures previously developed for heteronium ylid formation have been applied in the synthesis of selenonium ylides. A number of researchers² have utilized the "salt method" wherein a selenonium salt containing an acidic H on one of its substituent groups is treated with a base. Lloyd^{3a-c} has advanced the concept of ylid formation via the decomposition of a suitable diazo compound in the presence of a selenium-containing carbene scavenger. The treatment of a disubstituted selenium dihalide with a stabilized carbanion provided good yields of stabilized ylides.^{3d,4,5} Selenonium ylides have also been prepared by the reaction of selenoxides with active methylene compounds in the presence of desiccating agents.^{4h,j;6a} Finally, selenonium imides⁶ have been utilized in a mild ylid preparation.

The reactivity of a heteronium ylid depends in part upon the degree of carbanion stabilization supplied by the adjacent heteroatom. By analogy, with sulfur one would expect the empty d orbitals of Se to provide p-d π stabilization. X-ray crystallographic studies^{4b,5} indicated a definite fraction of double bond character although this was less than in analogous S ylides. This could be rationalized due to the greater diffuseness of 4d vs. 3d orbitals and the anticipated lower dipole interaction concomitant with the increasing bond lengths associated with heavier atoms.^{3c,4b} Consistent with this hypothesis was the bathochromic shift observed in the UV spectrum of λ_1 relative to its sulfur counterpart.^{3a} An examination of the carbonyl stretching vibrations for λ_2 indicated a -50 cm⁻¹ shift relative to the S analog.^{3d} These shifts could be explained by a greater anionic stabilization afforded by the sulfur derivatives.

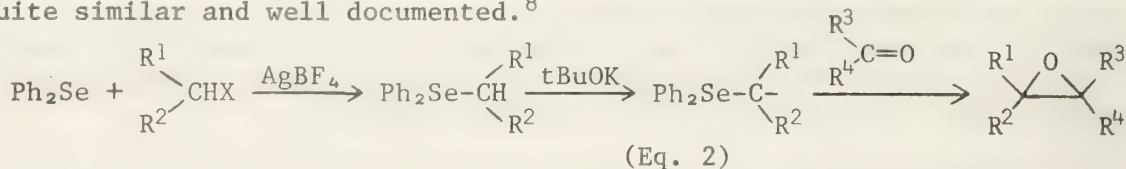


Lloyd³ examined the comparative reactivities of S and Se ylides in his work with heteronium tetraphenyl cyclopentadienylides. While no reaction was seen with p nitrobenzaldehyde, both the S and Se analogs underwent reaction with nitrosobenzene to yield nitrones.^{3b,c} (Eq. 1).

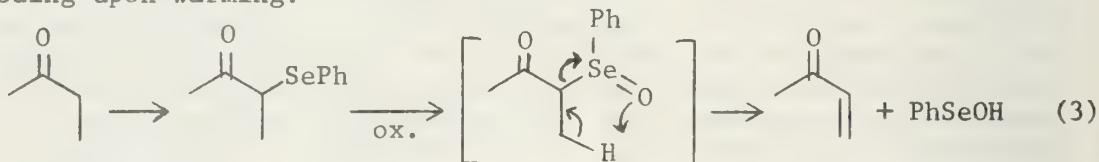


Magdesieva^{4e} was able to synthesize tetra substituted furans through the reaction of selenonium diketoylides with dimethyl acetylene dicarboxylate. A similar reaction had been obtained with sulfonium ylides.⁷

Only one unstabilized selenonium ylid has appeared in the literature.^{2b} Krief treated diphenyl selenide with an excess of alkyl halide in the presence of AgBF_4 to obtain selenonium salts. The corresponding ylides were generated *in situ* and were reacted with non-enolizable aldehydes and ketones to form epoxides (Eq. 2). The chemistry of non-stabilized sulfonium ylides is quite similar and well documented.⁸



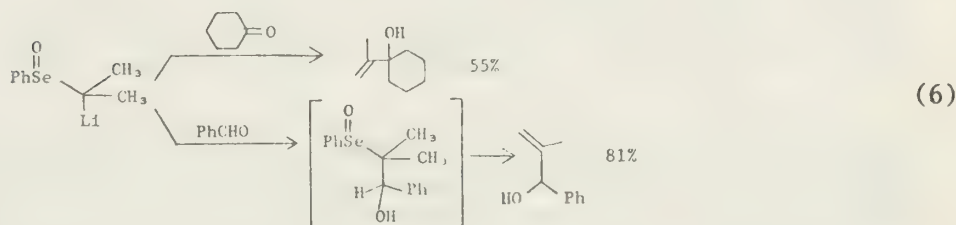
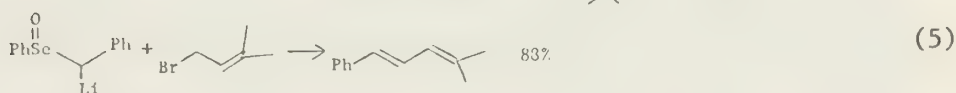
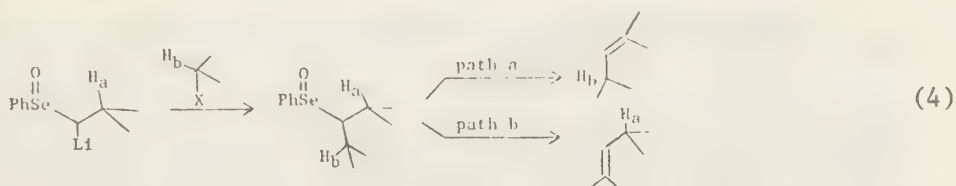
α Lithio Selenoxides. With the discovery by Jones⁹ that selenoxides undergo a facile elimination, these compounds have become versatile synthetic intermediates.¹⁰ This syn elimination^{11a} has been used for the dehydrogenation of ketones,^{10b;11b;12a,b;13a} esters,^{11b,12a} lactones^{11b,14} and nitriles¹⁵ (Eq. 3) at or below room temperature. One of the major facets of the utility of this reaction is the large number of methods available for the introduction of the phenylselenenyl group α to the desired functional group. Diphenyl diselenide, phenylselenenyl bromide and phenylselenenyl chloride have been used as electrophilic selenium species for the introduction of PhSe in enol acetates,^{10b,12a,13a} enol silanes,^{12a} nitrile anions¹⁵ and carbonions α to a carbonyl.^{11b;12a,b;14} The nucleophilic phenyl selenenyl anion has been used to introduce PhSe with α -halo esters,^{11a,b} α -halo ketones,^{10b} α -halo acids^{10a} and epoxides.^{11c} Additions of various selenium reagents to double bonds have afforded allylic alcohol precursors^{11d,12c,13b} while addition to acetylenes provided enone precursors.^{12c} In all of the above examples, the newly introduced selenides were oxidized at low temperatures with elimination ensuing upon warming.



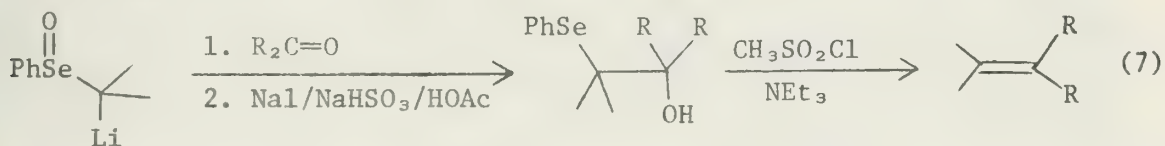
The previously mentioned methods of selenide introduction all involved a reaction which maintained an intact carbon skeleton. Reich^{12b,d,e} has recently explored the utilization of the selenoxide moiety for the stabilization of adjacent carbanions. This concept would effect a regiospecific introduction of the selenoxide and allow a convergent synthetic approach not afforded in the previous procedures. This use of a heterooxide for carbanion stabilization and subsequent elimination has precedent in sulfur chemistry. Trost¹⁶ has developed conditions for the alkylation of sulfoxide stabilized carbanions with a syn sulfoxide elimination performed on the products. The sulfoxide elimination, however, generally requires harsher conditions than for the Se analog.

In developing α -lithio selenoxide reagents for wide synthetic applications, several factors had to be considered. After reactions with electrophiles, the subsequent elimination (Eq. 4) could occur away from the newly formed C-C bond, with a product equivalent to a vinyl anion synthon (path a); alternatively, elimination occurring across the new C-C bond (path b) would be equivalent to the coupling of halides to form an olefin. To be synthetically useful, reactions of this type must thus have one pathway predominant. Reich^{12d} was able to find systems in which the exclusive operation of either path was achieved. For example, methylphenyl and benzylphenyl selenoxide carbanions could only undergo subsequent syn elimination across the C-C bond formed in the reactions with alkyl halides (Eq. 5). However, with 1°- and

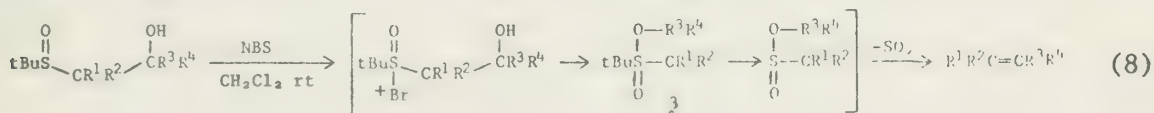
2°-alkyl phenyl selenoxide carbanions, both elimination pathways were potentially operative. The reaction products in these cases were found to be dependent upon the nature of the electrophile. Reaction with ketones could only give allyl alcohols, but an aldehyde electrophile could result in an allyl alcohol or an enol (Eq. 6). Solely observed was the elimination to allyl alcohols, a phenomenon also seen in the reaction products of nucleophilic selenium reagents with epoxides.^{11c} The reactions with allyl halides strongly favored elimination to the conjugated dienes, while saturated alkyl halides produced mixtures of olefins. Although methyl benzoate was used to form enones, the reactions of α-lithio selenoxides with aliphatic esters or benzoyl chloride did not give synthetically useful yields of enones.



Reich^{12e} found that β-hydroxy selenoxides, the reaction products of α-lithio selenoxides with carbonyls, could be reduced to β-hydroxy selenides under sufficiently mild conditions such that the syn selenoxide elimination was not a problem. When treated with methane sulfonyl chloride and triethylamine at room temperature, the β-hydroxy selenides were cleanly converted into olefins. (Eq. 7) The substituted olefins were produced in good yields with the double bond stereochemistry dependent upon the ratio of diastereomeric hydroxy selenides.

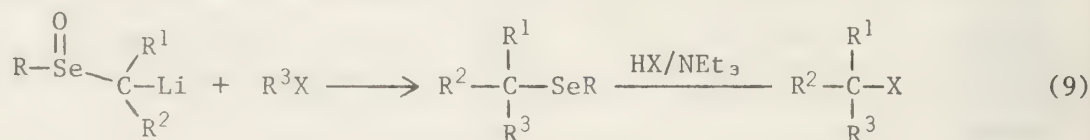


Durst¹⁷ recently developed a very mild analogous olefin formation utilizing β-hydroxy alkyl t-butyl sulfoxides derived from α-lithio sulfoxides and carbonyls. Treatment of the β-hydroxy sulfoxides with NCS or NBS at ambient temperatures formed the β-sulfonates which subsequently decomposed to olefins (Eq. 8). However, the method was limited by a dependence on the t-butyl substituent as a leaving group. In the synthesis of tetrasubstituted olefins ($\text{R}^1, \text{R}^2 = \text{alkyl}$) either 3°-alkyl could cleave and yields below 50% were maximally achieved.



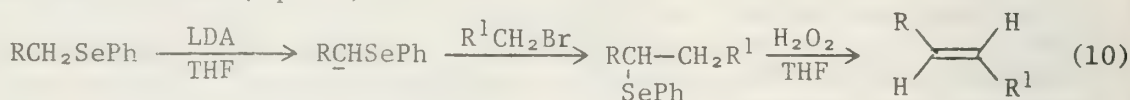
Krief¹⁸ has recently reported a room temperature conversion of selenoxides to alkyl halides (Eq. 9). Gaseous HX was bubbled into the selenoxide

solution at -78° for 30 seconds, triethyl amine was added, and the acidic solution was then slowly warmed to room temperature. In general, alkyl bromides were obtained faster and in higher yields than other alkyl halides. Possible mechanisms and the role of the amine in this transformation were not discussed. No such reaction has been reported for analogous sulfoxides.



α Lithio Selenides. Gilman^{19a} first uncovered the anomalous metalation properties of selenides when he noticed that diphenyl selenide underwent cleavage with *n*-butyllithium in ether rather than ortho nuclear metalation as observed in diphenyl sulfide. Similarly, with methyl phenyl selenides cleavage in *n*-butyllithium was predominant, while the analogous sulfides experienced exclusive lateral metalation.¹⁹ However, since the inception of the syn selenoxide elimination, Sharpless^{11b} and Greico¹⁴ have frequently employed carbanions α to both a phenylseleno and a carbonyl group. They were able to successfully avoid selenide cleavage through utilization of a lithium dialkyl amide base. Nevertheless, neither group has described the stabilization of a carbanion solely by an α -selenyl substituent.

Reich^{12d} and Mitchell²⁰ were able to laterally metalate phenyl benzyl selenide using LDA, although simple alkyl selenides were not deprotonated under similar conditions. This α -lithio selenide was reacted with various alkyl halides or cyclohexene oxide and the resultant products were oxidized to selenoxides, with subsequent elimination yielding a variety of phenyl substituted olefins (Eq. 10).



Reich²¹ found that lateral metalation was also possible in the case of variously substituted allyl phenyl selenides (Figure 1). The anions 4 - 8 were seen to be powerful nucleophiles as reactions with 1°-alkyl halides, epoxides, ketones, and trialkyl silyl chlorides were carried out at -78° and were complete within 15 minutes. However, as with allyl sulfide anions²² there was a problem of α vs. γ reaction. Although alkylation appeared to occur predominantly α , the reactions of other electrophiles gave more variable α/γ ratios with some of the anions (e.g., in reactions with 4, α/γ was 82/18 for trimethyl chlorosilane, 15/85 for acetophenone). While the allyl sulfide anion nonspecificity could be dealt with via substituent groups on S having chelating potential,²³ similar attempts with Se analogs did not increase α/γ substitution ratios. Thus, anions of 2-pyridyl allyl sulfide (9) showed improved α selectivity while 2-pyridyl allyl selenide (10) did not give increased α/γ ratios. Reich suggested that complexation with the diisopropyl amine present may have prevented the chelation of the lithium with the pyridine N.

Figure 1

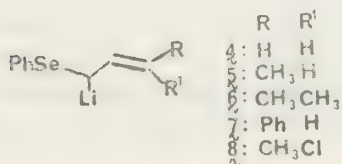
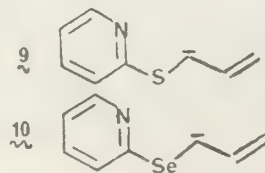
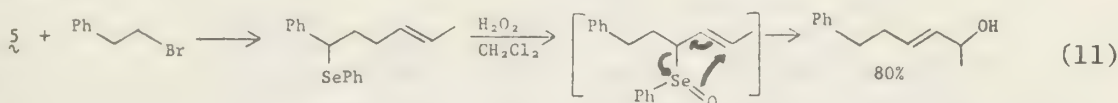


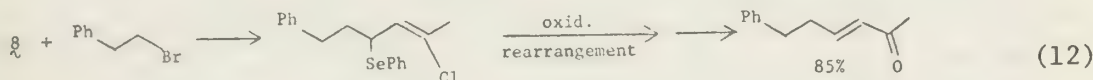
Figure 2



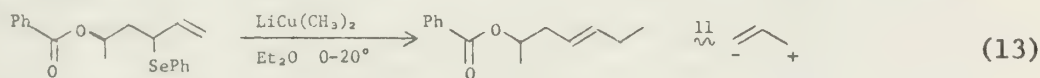
The alkylation products of allyl sulfide anions had been shown to undergo reductive cleavage²³ and corresponding allyl sulfoxides were known to undergo reversible (2,3) sigmatropic rearrangements²² to produce allylic alcohols. Reich²¹ developed the latter transformation for application to the reactions products of allyl selenide carbanions. Thus upon H₂O₂ oxidation, the intermediate selenoxide underwent a clean rearrangement to eventually give the allylic alcohol (Eq. 11). The allyl selenoxide shift proceeded more rapidly than syn selenoxide elimination, although a small amount of diene was observed in cases where elimination was enhanced by a substituent (e.g., phenyl).



The reaction products of the γ -methyl γ -chloro allyl carbanions (8) were particularly interesting because oxidation and rearrangement led to β -substituted methyl vinyl ketones (Eq. 12). The similar rearrangement of 3-chloro 2-buten-1-yl sulfoxide to methyl vinyl ketone had also been reported.²⁴

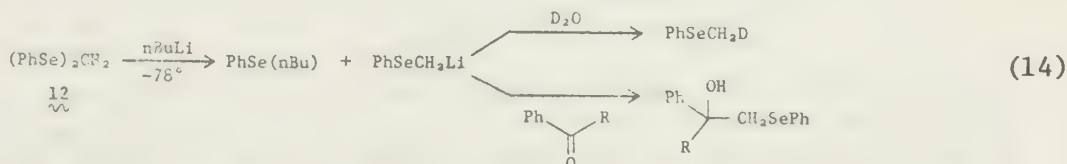


The reaction of allyl selenides with lithium dimethyl cuprate gave products in which the addition of a methyl group had caused displacement of the PhSe substituent (Eq. 13). Using allyl selenenyl carbanions, the interesting allyl synthon 11 was thus available.



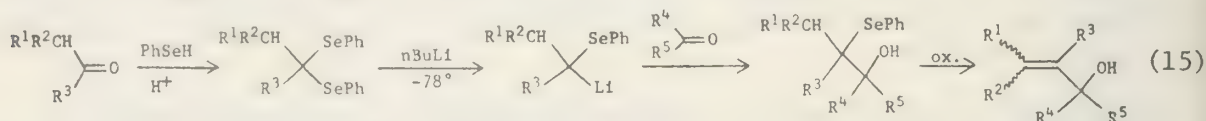
The synthetic use of α -lithio sulfides or selenides appeared to be limited primarily by the methods of carbanion generation available. Phenyl alkyl sulfide utilization was limited by the ortho nuclear metalation that occurred with homologues higher than methyl.^{18b} As discussed previously, phenyl alkyl selenides only underwent deprotonation with lithium dialkyl amides when the alkyl group was an "activating" benzyl or allyl. Simpler alkyl selenides did not deprotonate with LDA and were cleaved by alkyl lithium reagents.

Seebach^{25a,b} cleverly exploited this Se-C bond lability for the preparation of selenium stabilized carbanions. Thus, bis(phenylseleno)methane (12) underwent facile cleavage with *n*-butyllithium to produce phenylselenomethyl-lithium (Eq. 14). Similar reaction of tris(phenylseleno)methane, however, led to a mixture of bis and tris(phenylseleno) methyl-lithium, while tetra-seleno orthocarbonate underwent cleavage solely to tris(phenylseleno) methyl-lithium. The existence of these anions was proved through the isolation of their reaction products with D₂O, benzaldehyde or methyl iodide. Of the analogous S compounds, only the tetrathioorthocarbonates underwent S-C bond cleavage.^{25c}

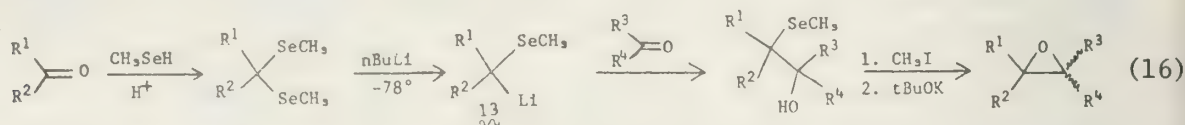


Because selenoacetals and ketals could be formed from either diiodo or carbonyl compounds, the generation of α -seleno carbanions via an alkyl-lithium

cleavage provided a pathway to hitherto inaccessible selenium reagents. Krief^{26a} and Seebach^{25d} both used this method to generate α -seleno carbanions, which they reacted with various carbonyl compounds. Although β -hydroxy selenides had previously been obtained from the ring opening of epoxides^{11c} with selenophenolate anion, unsymmetrically substituted epoxides could furnish two different products. This ambiguity was avoided since the exact nature and position of all of the substituents could be controlled in the method of Krief and Seebach (Eq. 15).

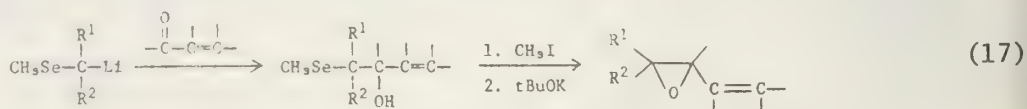


With this facile generation of β -hydroxy selenides available, several new reactions of these compounds were developed. Krief^{26b,f} developed a mild synthesis of epoxides from these intermediates. Using AgBF_4 and methyl iodide, β -hydroxy selenonium salts were formed, which upon treatment with base in DMSO underwent displacement of methyl phenyl selenide to yield the epoxide. An improved epoxide synthesis was later reported utilizing methyl rather than phenyl selenoacetals. Krief^{26c} found that the nucleophilicity of the Se atom in the resultant β -hydroxy methyl selenides was higher than in the corresponding phenyl compounds, thus obviating the use of AgBF_4 in the salt formation step (Eq. 16). Thus, α -methylseleno carbanions **13** did not equilibrate under experimental conditions and displayed a high nucleophilicity with carbonyl compounds, including enolizable or hindered examples. Epoxides could be obtained in good yields without isolation of the β -hydroxy selenide or selenonium intermediates.



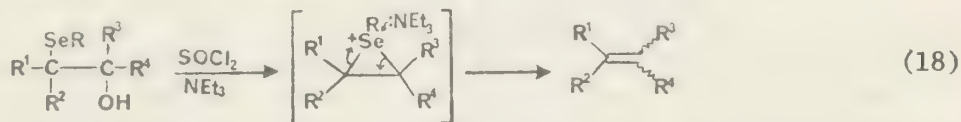
The standard sulfur method of ketone to epoxide conversion normally involves a sulfonium or sulfoxonium ylide.⁸ However, since this method has occasionally failed due to steric hindrance or enolization of the substrate, Coates²⁷ has developed a mild method using phenylthiomethyl lithium. By generation of the β -hydroxy sulfonium salt, followed by reaction in base, terminal epoxides were formed in good yields. This method was limited, however, since homologues of phenyl methyl sulfide underwent ortho nuclear metalation.

While alkylidene transfer from a sulfur ylide⁸ to an α,β -unsaturated carbonyl has been a powerful route to α,β -unsaturated epoxides, the method has found wide application only in the methylene case. Krief^{26d} thus addressed this limitation and was able to extend his previous work with α -seleno carbanions into a regiospecific synthesis of α,β -unsaturated epoxides (Eq. 17). The selenium stabilized carbanions reacted with a high propensity on the carbon-oxygen bond, leading specifically to γ,δ -unsaturated β -hydroxy selenide. Tetrasubstituted epoxides could then be formed as before or, alternatively, a syn selenoxide elimination could be effected to yield β,γ β',γ' unsaturated alcohols.



β -Hydroxy selenides were also found to be viable precursors to alkenes. Reich,^{12e} as mentioned earlier, had successfully developed a β -hydroxy selenoxide to selenide to olefin transformation. Krief^{26f} found that β -hydroxy selenides could be converted to olefins via: pTsOH /pentane/reflux; HClO_4 /ether/25 ; or with more sensitive compounds, trifluoroacetic anhydride/

$\text{CH}_2\text{Cl}_2/\text{NEt}_3$. Under these conditions, the transformation was highly stereoselective and occurred formally by the trans elimination of hydroxy and selenyl moieties. Through use of the reaction of α -seleno carbanions with carbonyls, the double bond could be regiospecifically introduced as well. In later work, Krief^{26g} settled upon $\text{SOCl}_2/\text{NEt}_3$ in dichloromethane as the reagents of choice for this transformation. The reaction occurred readily at room temperature and produced even tetra substituted olefins. As with the above cases, a mechanism involving a seleniranium ion²⁸ was proposed to account for the observed stereoselectivity of the reaction (Eq. 18).



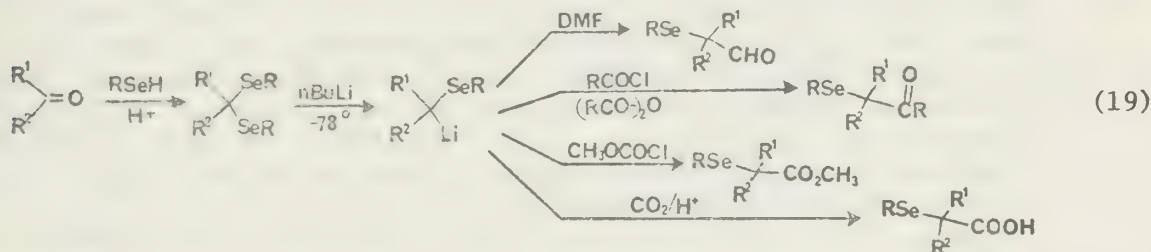
The analogous conversion of β -hydroxy sulfides to olefins was accomplished by Coates,²⁹ using a reductive elimination of phenylthio methyl carbonyl esters. Kuwajima³⁰ also effected this transformation by the decomposition of the phosphites formed from the reaction of *o*-phenylene phosphorochloridite with β -hydroxy sulfides. Both methods, however, were limited to ketone methylenations since homologues of methyl phenyl sulfide could not be laterally metalated.

Selenium stabilized carbanions were also found to undergo reaction with various alkyl halides. These product selenides could then be reduced to alkanes through the use of typical sulfide reducing agents.³¹

Selenides derived from α -seleno carbanion reactions also underwent displacement by halogens. Krief^{26h} observed that 2°- or 3°-alkyl methyl selenides were converted in good yields to 2°- or 3°-alkyl bromides by reaction with bromine or NBS in aqueous ethanol at room temperature. However, 1°-alkyl methyl selenides reacted poorly under these conditions. For these 1°-alkyl selenides, Krief thus used a complementary method involving the formation of the dimethyl alkyl selenonium salt and subsequent displacement with NaI in DMF. Corey³² had previously applied this latter procedure in the preparation of iodides from phenyl sulfides.

By applying the above halogenation reactions to β -hydroxy selenides, Krief obtained a regiospecific synthesis of bromohydrins. Oxidation of 2° hydroxy groups thus could provide a regiospecific route to α -bromo ketones.

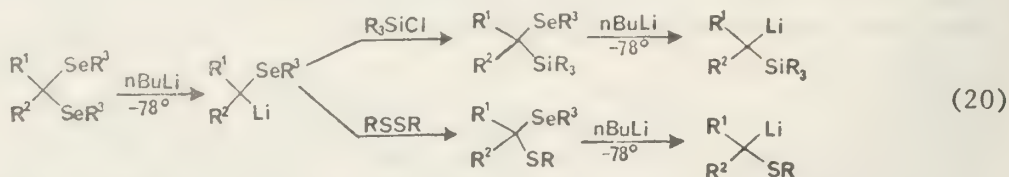
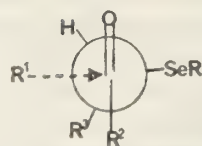
Besides their facile reactions with aldehydes, ketones and alkyl halides, selenyl alkylolithium reagents have also been used to produce α -seleno aldehydes, α -seleno ketones, α -seleno esters and α -seleno acids in synthetically useful yields (Eq. 19). A syn selenoxide elimination was then used for the regiospecific formation of α,β -unsaturated carbonyls.



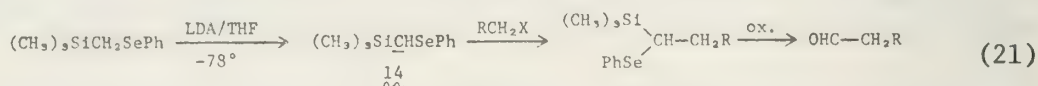
Krief^{26e} also used these α -seleno aldehydes and ketones in reactions with hydrides and organometallics.³³ These additions occurred stereoselectively and thus provided a regiospecific and stereoselective pathway to

olefins and epoxides. The high selectivity of these reactions was explained by invocation of the Felkin model³⁴ (Figure 3) in which the separation between the selenenyl group and the incoming organometallic is the greatest. In agreement with this hypothesis, the more polar selenophenyl group led to better stereochemical control (erythro/threo: 94/6) than did the selenomethyl group (erythro/threo: 85/15).

Figure 3



The chemistry of mixed silyl or sulfo selenyl acetals has recently developed due in a large part to the emergence of selenium stabilized carbanions. These mixed acetals had previously been obtained via the reaction of selenophenolate anion with a vinyl sulfide or with an α -halo sulfide^{35a} or silane.^{35a,36} However, the reactions of α -seleno carbanions with trialkyl silyl chlorides³⁵ or diphenyl disulfide^{35a,b;25d} proved to be a more facile route (Eq. 20). 1-Trimethylsilyl 1-phenylseleno methyllithium (14) was generated with LDA in THF at -78° or through the use of *sec*-butyllithium - TMEDA at room temperature. This carbanion was then alkylated with 1°-halides and the products oxidized to the corresponding aldehydes in good yields³⁶ (Eq. 21).



Another clever use of mixed silyl or sulfo selenyl acetals utilized the known lability of the Se-C bond. Thus treatment of these acetals with *n*-butyllithium selectively cleaved an alkyl selenide to leave an α -silyl or α -sulfo carbanion. This method was used to prepare previously inaccessible silyl and sulfo lithium reagents which could then undergo typical reactions to epoxides and alkenes³⁷ (Eq. 20).

BIBLIOGRAPHY

- (a) N. Zefirov, *Chemica Scripta*, 8A, 20 (1975); (b) D. Lloyd, *ibid.*, 8A, 14 (1975).
- (a) E. D. Hughes and K. I. Kuriyan, *J. Chem. Soc.*, 1609 (1935); (b) W. Dumont, P. Bayet, and A. Krief, *Angew. Chem. Internat. Ed.*, 13, 274 (1974); (c) W. Lotz and J. Gosselk, *Tetrahedron*, 29, 917 (1973).
- (a) D. Lloyd and M. Singer, *Chem. Commun.*, 390 (1967); (b) D. Lloyd and M. Singer, *Chem. Ind. (London)*, 1277 (1968); (c) B. Freeman, D. Lloyd, and M. Singer, *Tetrahedron*, 28, 343 (1972); (d) E. Ernstbrunner and D. Lloyd, *Ann. Chem.*, 753, 196 (1971).
- (a) N. Magdesieva, *J. Org. Chem. USSR*, 7, 2316 (1971); (b) N. Magdesieva, *Dokl. Akad. Nauk. SSSR*, 206, 1130 (1972); (c) N. Magdesieva, *J. Organomet. Chem.*, 42, 399 (1972); (d) N. Magdesieva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 22, 647 (1973); (e) N. Magdesieva, *Chem. of Hetero. Compounds*, 1307 (1973); (f) N. Magdesieva, *J. Gen. Chem. USSR*, 44, 1677 (1974); (g) N. Magdesieva, *J. Org. Chem. USSR*, 9, 1778 (1973); (h) N. Magdesieva, *ibid.*, 11, 505 (1975); (i) N. Magdesieva, *ibid.*, 11, 2636 (1975); (j) N. Magdesieva, *ibid.*, 12, 33 (1976).
- K. Wei, I. C. Paul, M. Chang, and J. I. Musher, *J. Am. Chem. Soc.*, 96, 4099 (1974).
- (a) S. Tamagaki and K. Sakaki, *Chem. Letters*, 503 (1975); (b) S. Tamagaki, I. Hatanaka, and K. Tamura, *ibid.*, 81 (1976); (c) S. Tamagaki

- and I. Hatanaka, *ibid.*, 301 (1976); (d) S. Tamagaki and I. Hatanaka, *ibid.*, 1303 (1976).
7. Y. Hayashi, H. Kobayashi, and H. Nozaki, *Tetrahedron*, 26, 4353 (1970).
8. B. M. Trost and L. S. Melvin, "Sulfur Ylides," Academic Press, N.Y. (1975).
9. D. Jones, D. Mundy, and R. Whitehouse, *J. Chem. Soc. Chem. Commun.*, 86 (1970).
10. (a) K. Sharpless, *Chemica Scripta*, 8A, 9 (1975); (b) H. Reich, J. Renga, and I. Reich, *J. Am. Chem. Soc.*, 97, 5434 (1975).
11. (a) K. Sharpless, M. Young, and R. Lauer, *Tetrahedron Lett.*, 1979 (1973); (b) K. Sharpless, R. Lauer, and A. Teranishi, *J. Am. Chem. Soc.*, 95, 6137 (1973); (c) K. Sharpless and R. Lauer, *ibid.*, 95, 2697 (1973); (d) K. Sharpless and R. Lauer, *J. Org. Chem.*, 39, 429 (1974).
12. (a) H. Reich, I. Reich, and J. Renga, *J. Am. Chem. Soc.*, 95, 5813 (1973); (b) H. Reich, J. Renga, and I. Reich, *J. Org. Chem.*, 39, 2133 (1974); (c) H. Reich, *ibid.*, 39, 428 (1974); (d) H. Reich and S. Shah, *J. Am. Chem. Soc.*, 97, 3250 (1975); (e) H. Reich and F. Chow, *JCS Chem. Commun.*, 790 (1975).
13. (a) D. L. Clive, *J. Chem. Soc. Chem. Commun.*, 695 (1973); (b) D. L. Clive, *JCS Chem. Commun.*, 100 (1974).
14. P. Grieco and M. Miyashita, *J. Org. Chem.*, 39, 120 (1974).
15. D. Brattesani and C. Heathcock, *Tetrahedron Lett.*, 2279 (1974).
16. For example: B. Trost and T. Salzmann, *J. Org. Chem.*, 40, 148 (1975).
17. F. Jung, N. Sharma, and T. Durst, *J. Am. Chem. Soc.*, 95, 3420 (1973).
18. L. Hevesi, M. Sevrin, and A. Krief, *Tetrahedron Lett.*, 2651 (1976).
19. (a) H. Gilman and R. Bebb, *J. Am. Chem. Soc.*, 61, 109 (1939); (b) H. Gilman and F. Webb, *ibid.*, 71, 4062 (1949).
20. R. Mitchell, *JCS Chem. Commun.*, 990 (1974).
21. H. Reich, *J. Org. Chem.*, 40, 2570 (1975).
22. D. Evans and G. Andrews, *Accounts Chem. Res.*, 7, 147 (1974).
23. For example see: T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 259 (1972).
24. P. Lansbury and J. Rhodes, *Chem. Commun*, 21 (1974).
25. (a) D. Seebach and N. Peleties, *Angew. Chem. Int. Ed. Eng.*, 8, 450 (1969); (b) D. Seebach and N. Peleties, *Chem. Ber.*, 105, 511 (1972); (c) D. Seebach, *Angew. Chem. Int. Ed. Eng.*, 6, 442 (1967); (d) D. Seebach and A. Beck, *ibid.*, 13, 806 (1974).
26. (a) W. Dumont, P. Bayet, and A. Krief, *Angew. Chem. Int. Ed. Eng.*, 13, 804 (1974); (b) W. Dumont and A. Krief, *Angew. Chem.*, 87, 347 (1975); (c) D. VanEnde, W. Dumont, and A. Krief, *Angew. Chem. Int. Ed. Eng.*, 14, 700 (1975); (d) D. VanEnde and A. Krief, *Tetrahedron Lett.*, 457 (1976); (e) A. Leonard-Coppens and A. Krief, *ibid.*, 3227 (1976); (f) J. Remion, W. Dumont and A. Krief, *ibid.*, 1385 (1976); (g) J. Remion and A. Krief, *ibid.*, 3743 (1976); (h) M. Sevrin, W. Dumont, L. Hevesi, and A. Krief, *ibid.*, 2647 (1976); (i) M. Sevrin, D. VanEnde, and A. Krief, *ibid.*, 2643 (1976); (j) J. Denis, W. Dumont, and A. Krief, *ibid.*, 453 (1976).
27. J. Ollinger and R. M. Coates, *J. Am. Chem. Soc.*, 95, 3429 (1973).
28. G. Schmid and D. Garratt, *Tetrahedron Lett.*, 3991 (1975).
29. R. L. Sowerby and R. M. Coates, *J. Am. Chem. Soc.*, 94, 4758 (1972).
30. I. Kuwajima, S. Sato, and Y. Kunata, *Tetrahedron Lett.*, 737 (1972).
31. H. House, "Modern Synthetic Reactions," 2nd Edition, W. A. Benjamin, 1972.
32. E. J. Corey and M. Jautelat, *Tetrahedron Lett.*, 5787 (1968).
33. Grignard reagents did not add to α -seleno ketones under standard conditions.
34. M. Cherist, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968).
35. (a) A. Anciaux, W. Dumont, D. VanEnde, and A. Krief, *Tetrahedron Lett.*, 1613 (1975); (b) A. Anciaux, A. Eman, W. Dumont, and A. Krief, *ibid.*, 1617 (1975); (c) W. Dumont and A. Krief, *Angew. Chem. Int. Ed. Eng.*, 15, 161 (1976).
36. K. Sachdev and H. Sachdev, *Tetrahedron Lett.*, 4223 (1976).
37. For the silyl case see: Craig Kubitschek, Univ. of Ill. organic seminar, Nov. 15, 1976.

RECENT ORGANIC SYNTHETIC TRANSFORMATIONS VIA OXYTHALLATION

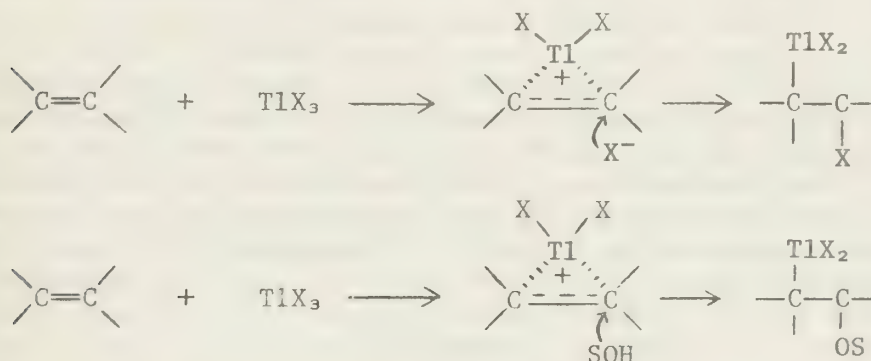
Reported by William Y. Lam

May 5, 1977

Introduction

Oxythallation is the overall addition reaction that occurs when an electrophilic thallium(III) salt reacts with a nucleophilic non-aromatic organic substrate, such as an olefin (Scheme I).

Scheme I



Generally, if X in TlX₃ is poorly nucleophilic, then a nucleophilic solvent (usually hydroxyl solvent), SOH, may participate at the thallinium ion stage and the net result is solvotherallation (oxythallation). The oxythallation adducts thus formed are, however, usually unstable and highly reactive intermediates which undergo rapid decomposition via C-Tl bond heterolysis to give a thallium(I) salt, and carbonium ion or carbonium ion-like species, the ultimate fate of which depends upon the nature of X, the structure of the organic substrate, and the reaction conditions, especially the solvent.

Oxythallation-dethallation of olefins has been studied for many years. The results of these investigations have mainly led to some understanding of the mechanism and stereochemistry of oxythallation; few reactions of preparative significance have been discovered. Kitching^{1a} in his review of oxythallation (1968) mentions little about the synthetic utility of the oxythallation-dethallation reactions. In the last several years, many papers have been published illustrating the usefulness of oxythallation in the synthetic transformations of some organic compounds. This abstract is mainly concerned with the simple and rapid reactions of a variety of organic substrates with thallium(III) salts via oxythallation to give specific transformation products which are potentially of synthetic use. Mechanisms of these transformations will be discussed. The topic will be restricted only to carbon-carbon multiple bonds as the nucleophilic substrates. The reactions with carbon-carbon double bonds will be reviewed first.

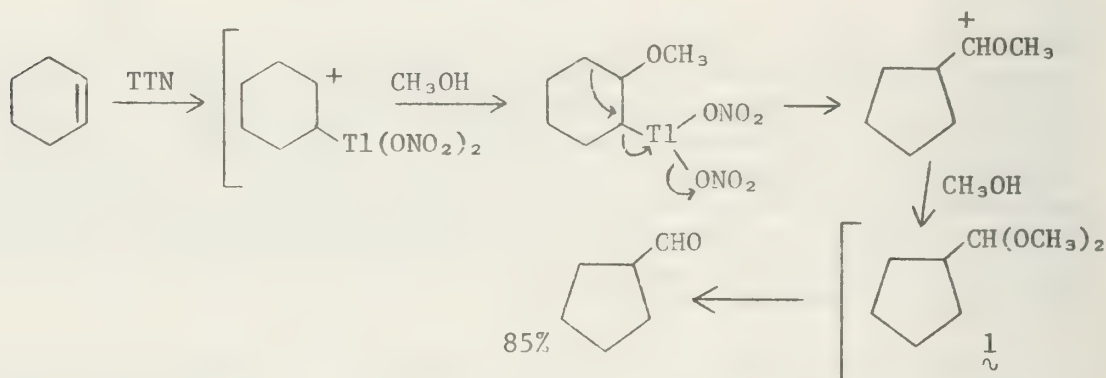
Reaction with Alkenes

1. Syntheses of Aldehydes and Ketones. Most olefins readily react with thallium(III) salts in the presence of dilute mineral acids, alcohols, and carboxylic acids to give the corresponding oxythallation adducts, which

can undergo dethallation to give either carbonyl or glycol derivatives. A variety of thallium(III) salts have been employed, including acetate, trifluoroacetate, perchlorate, and nitrate. Earlier examples of oxythallation of olefins with thallium(III) acetate (TTA) had little preparative significance due to the formation of mixture of products, which were frequently difficult to separate.¹ Kruse and Bednarski² have demonstrated that control over product distribution can be achieved by appropriate control of solvent. Thus, for example, oxidation of propylene with TTA in 50% v/v aqueous acetic acid gave a 1:1 mixture of propylene oxide and acetone; in the less polar medium 70% THF, 20% water, and 10% acetic acid, propylene oxide was obtained in 72% together with 16% acetone and 12% 1-acetoxy-2-propanol.

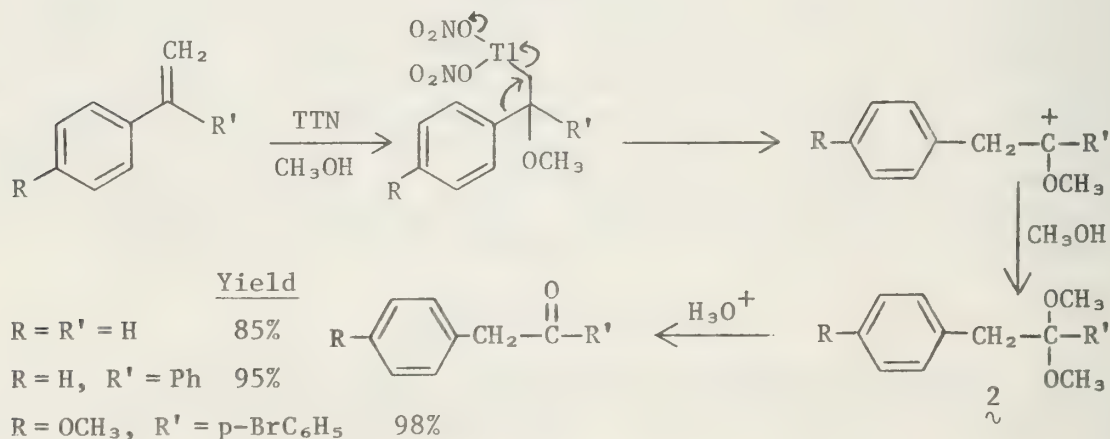
Oxidation of simple olefins by other thallium(III) salts have been reported^{3,4} to give high yields of a variety of aldehydes and ketones. Cyclic olefins undergo oxidative rearrangement to ring-contracted aldehydes or ketones; styrenes rearrange to arylacetaldehydes. Taylor and coworkers have developed a general synthetic method for these transformations. Using thallium(III) nitrate (TTN) in methanol or in dilute mineral acids, oxidative rearrangement of many olefins occurs at room temperature in a matter of minutes. With cyclohexene, for example, precipitation of thallium(I) nitrate was completed in 1 min at room temperature, and cyclopentane-carboxaldehyde was formed in 85% yield. The mechanism of this conversion is outlined in Scheme II.

Scheme II

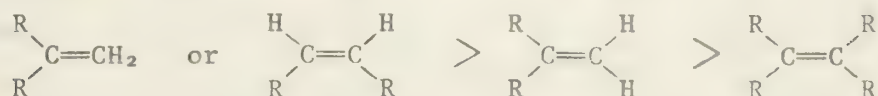


In the case of styrenes, the reduction of $Tl(III) \rightarrow Tl(I)$ is accompanied by aryl migration (Scheme III).

Scheme III



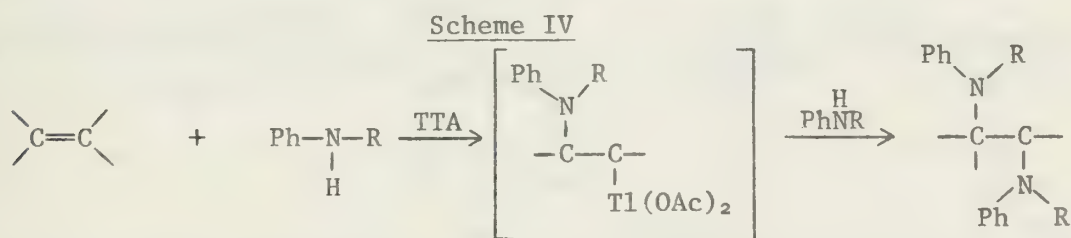
Reaction rates were found to depend on the degree of olefin substitution. Reactivity trends are illustrated as follows:



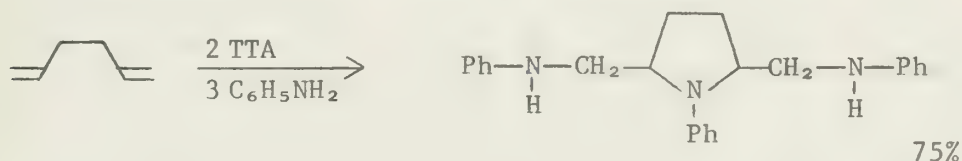
There was effectively no reaction with tetra-substituted olefins such as 1,1-diphenyl-2,2-dimethylethylene, whereas tetraalkyl olefins generally gave mixture of products. Low *et al.*⁵ recently reported that this oxidative rearrangement did not occur with exocyclic olefins; instead, allylic nitrates or their transformation products were isolated. The utility of TTN for the preparation of otherwise difficultly accessible compounds from materials which are readily available has been demonstrated by other workers.⁶ Other recent reports on oxythallation of olefins are, however, of mechanistic and stereochemical interests rather than that of synthetic.⁷

Taylor *et al.*⁸ recently have shown that the acetals 1 and 2 ($\text{R}=\text{R}'=\text{H}$) formed in the oxidative rearrangement of cyclohexene and styrene via oxythallation can be easily obtained in high yield by TTN supported on K-10 montmorillonite clay. Thus 1 and 2 were obtained in 85% and 91% yield respectively at room temperature in <1 min. The TTN/K-10 reagent was readily prepared by stirring K-10 clay with a solution of TTN in a mixture of methanol and trimethyl orthoformate followed by evaporation to dryness and was claimed as a remarkably efficient reagent for the rapid, selective, high yield, room temperature oxidation of a variety of unsaturated organic substrates.

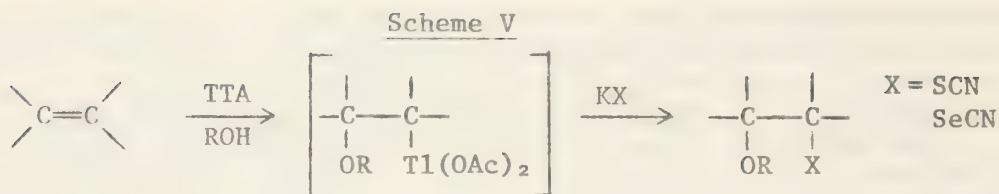
2. Synthesis of Amines. Nucleophilic nitrogen containing solvents can replace the usual oxygen containing solvents such as acetic acid and alcohol and participate in the oxythallation-dethallation reactions. Barluengen⁹ obtained a number of amines in good yield from the addition of anilines to alkenes in the presence of TTA (Scheme IV). Under the same reaction conditions, however, primary aliphatic amines do not add to alkenes.



For example, 1,4-hexadiene in the presence of TTA leads to the formation of 2,5-bis(anilino-methyl)-1-phenyl pyrrolidine:



3. Addition of Olefins. Substitution of the thallium moiety in oxythallation adducts of olefin by Cl, Br, CN,^{10a} SeCN,^{10b} and SCN^{10a,11} has been reported. Oxythiocyanation¹¹ and oxyselecyanation,^{10b} for example, were achieved *in situ* according to Scheme V.

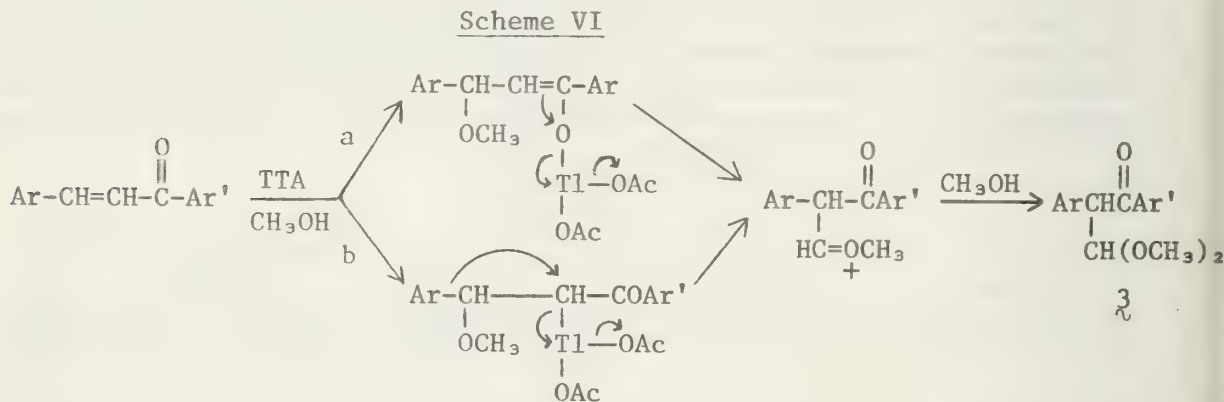


The reaction, however, went smoothly only with terminal olefins.

Decomposition of stable oxythallation adducts of olefins has been studied by some workers.¹² However, a mixture of products frequently of low yield, has usually resulted.

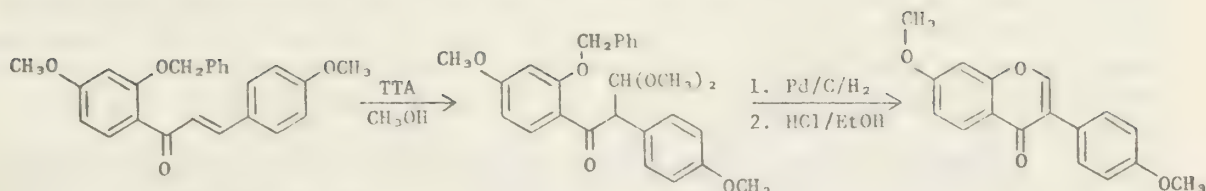
Reactions with α,β -Unsaturated Carbonyl Compounds

1. Oxidation of Chalcones. Owing to resonance delocalization in these systems, the carbon-carbon double bonds are significantly less nucleophilic than those of simple, isolated carbon-carbon double bonds. Consequently, reaction of such olefins with thallium(III) salts are much slower and little information is available on the oxythallation of α,β -unsaturated ketones. In 1966, Uemura¹³ stated that α,β -unsaturated ketones did not react with thallium(III) salts, but this conclusion was later shown to be incorrect. In 1970, Ollis and coworkers¹⁴ reported that prolonged treatment of highly activated chalcones (Scheme VI) with TTA in methanol resulted in oxidative rearrangement similar to that observed with simple olefins, as shown by formation of the acetal **3**. The involvement of 1,2-aryl migration in the reaction was proved by standard ¹⁴C labeling experiments.



The two most probable mechanisms which are consistent with Ollis's results are shown in Scheme VI (path a and b), but it is not known which of these is preferred. Compounds of the type **3** are potentially useful intermediates for the synthesis of many heterocyclic and carbocyclic systems. Thus, when suitably substituted chalcones were used as starting material (e.g., Scheme VII), these acetals could readily be converted into isoflavones. The synthetic utility of this interesting transformation was, however, severely limited due to relatively long reaction times and low yields (only 15%) of **3**.

Scheme VII

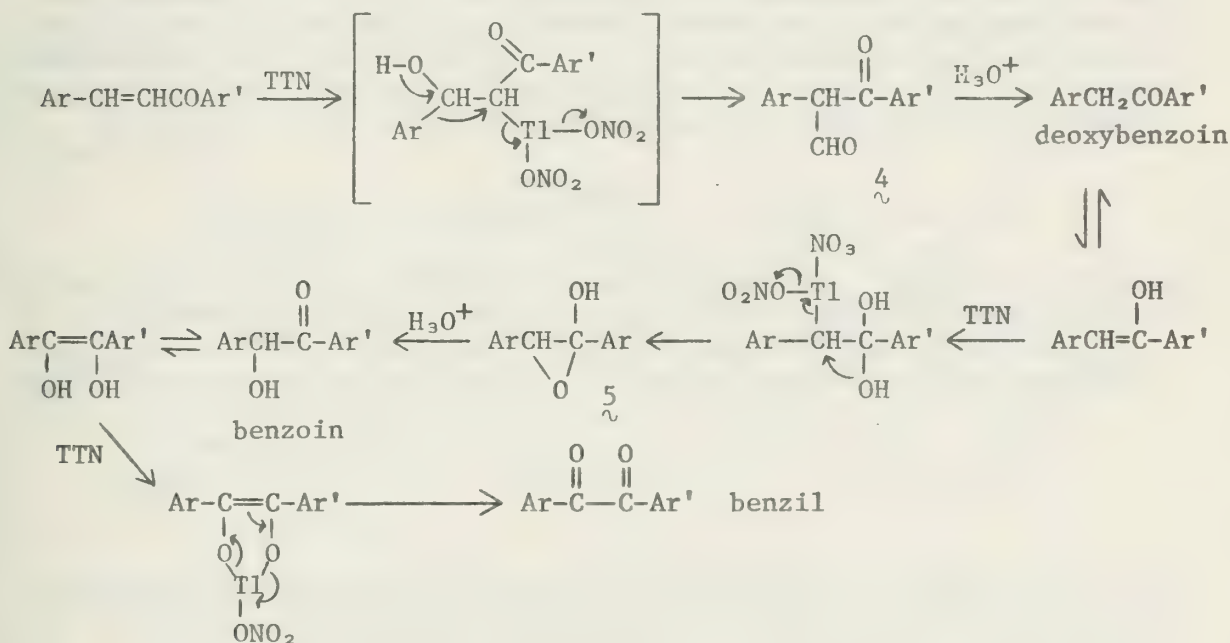


Farkas *et al.*¹⁶ later have extended the Ollis procedure into a simple and effective method for the preparation of isoflavones by using TTN rather than TTA. A number of isoflavonoids have subsequently been synthesized by this method.¹⁷

Taylor and coworkers¹⁸ recently reported that oxidative rearrangement of chalcones occurred smoothly in a solution of TTN in either trimethyl orthoformate alone or trimethyl orthoformate/methanol. High yields of the acetals (3) could be obtained. The acetal 3 ($\text{Ar} = 4\text{-CH}_3\text{OC}_6\text{H}_5$, $\text{Ar}' = 3\text{-O}_2\text{NC}_6\text{H}_5$), for example, was obtained from the corresponding chalcones in 93% yield.

Oxidation of chalcones with TTN has been studied in detail¹⁹ and it has been shown that the products obtained depend on the amount of reagent and the solvent employed. Oxidation with 1 equiv. of TTN in methanol, methanol-chloroform, or methanol-boron trifluoride leads to the acetals of the type 3 in yields of 20-80%. When 3 equiv. of TTN are employed, however, and aqueous glyme containing a little perchloric acid is used as solvent, the products are benzils. In this transformation, three distinct oxidation steps are involved, one carbon atom is lost, and the overall mechanism is shown in Scheme VIII.

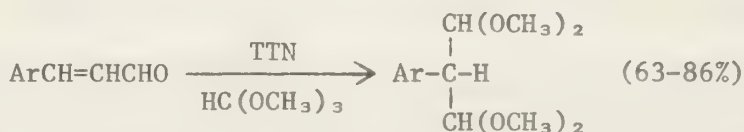
Scheme VIII



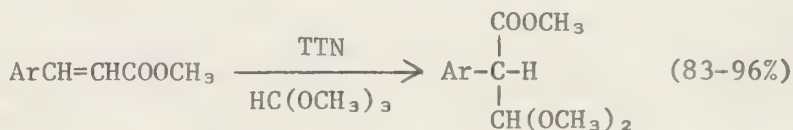
Oxidative rearrangement via oxythallation of the chalcone gives the β -aldehyde ketone 4, which, under the acidic reaction conditions, undergoes retro-Claisen condensation and gives the corresponding deoxybenzoin. Acid-

catalyzed enolization of this latter intermediate followed by hydroxythallation and intramolecular displacement of the thallium substituent leads to α -hydroxyepoxide (5), hydrolysis of which gives a benzoin. Oxidation of the benzoin via the ene-diol tautomer then gives the benzil. Independent oxidations of deoxybenzoins and benzoins,¹⁹ which are involved in the mechanism as intermediates, indeed result in the formation of benzils.

2. Oxidative Rearrangements of α,β -Unsaturated Aldehydes and Esters. Smooth oxidative rearrangement of chalcones via oxythallation with TTN in trimethyl orthoformate have been reviewed earlier. Analogous reactions occur with other types of α,β -unsaturated carbonyl compounds. Thus, cinnamaldehydes undergo smooth oxidation to give phenyl malonaldehyde bis-dimethyl acetals:



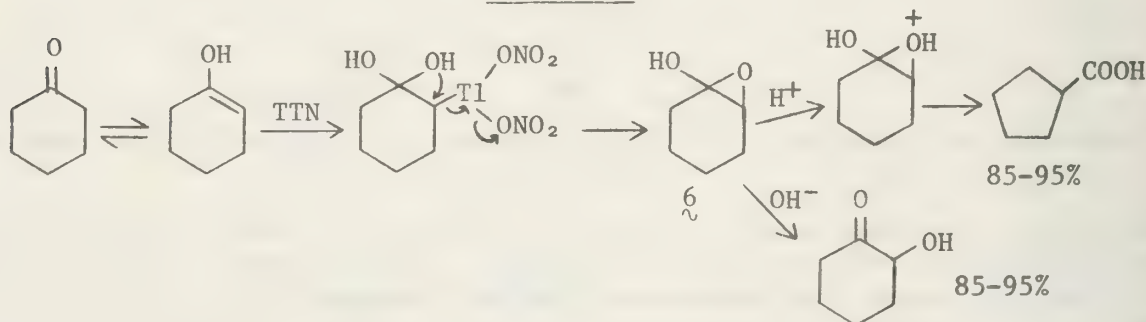
Cinnamic esters are converted into the corresponding β -aldehyde-ester dimethyl acetals:^{8,18}



Reaction with Carbonyl Compounds

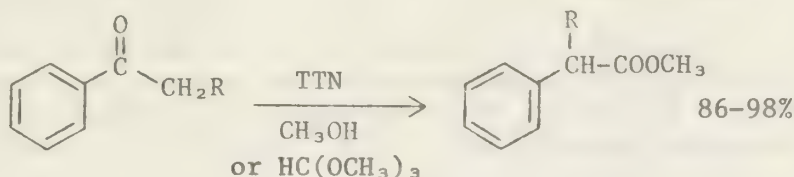
1. Oxidation of Ketones. Carbonyl compounds which enolize under acidic conditions are also readily oxidized by thallium(III) salts. Oxidation of cyclohexanone has been studied earlier by several workers.²⁰ However, the mechanism was uncertain and the yield of the products was not of preparative significance. Taylor *et al.*²¹ have proposed a most probable mechanism according to their findings (Scheme IX). The products formed from the oxidation of cyclohexanone by TTN in acetic acid is found dependent on the isolation procedure employed.

Scheme IX



The reaction sequence is enolization, hydroxythallation and subsequent intramolecular nucleophilic displacement of the thallium substituent to give the intermediate 6, from which the final products are derived. Synthetic utility of this transformation has been reported by Romeo and Ortar.²²

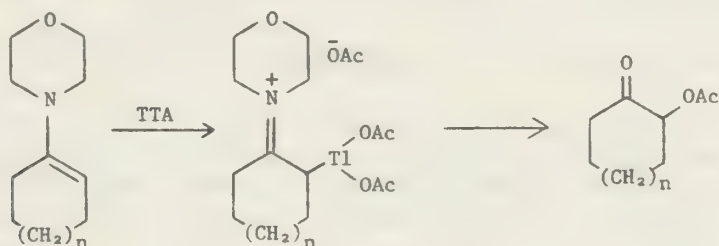
Aryl alkyl ketones easily undergo oxidative rearrangements via oxythallation to give the corresponding methyl arylacetates in excellent yield:^{8,18,23}



This reaction has also been used for the preparation of a key pyrrole intermediate in the synthesis of porphobilinogen.²⁴

2. Oxidation of Enamines. As might be expected on the basis of the above results, enamines react smoothly with thallium(III) salts. Enamines of cycloalkanones yield α -acetoxy derivatives when treated with TTA in acetic acid (Scheme X).²⁵

Scheme X



Reaction with Alkynes

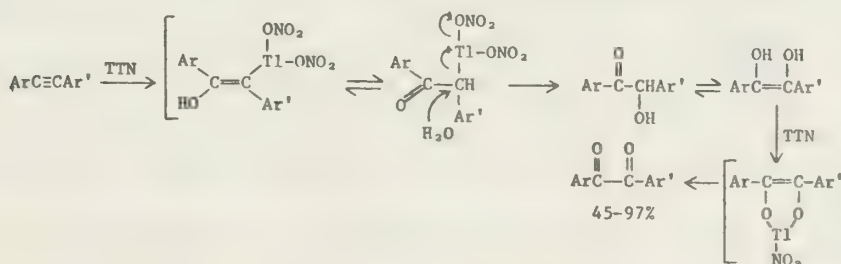
Taylor and coworkers²⁶ have systematically examined the oxidations of acetylenes with TTN. Prior to this work, there was only one report in the literature on the topic.²⁷

Oxidation of diarylacetylenes with two equiv. of TTN gives benzils in good yield:

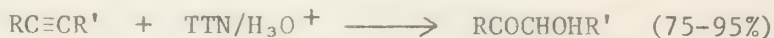


Hydroxythallation of the $\text{C}\equiv\text{C}$ bonds leads to an enolic intermediate (Scheme XI): displacement of the thallium moiety from the keto tautomer results in the formation of a benzoin, which is oxidized to the corresponding benzil by the second equivalent of TTN in the same way as was described before (see Scheme VIII).

Scheme XI

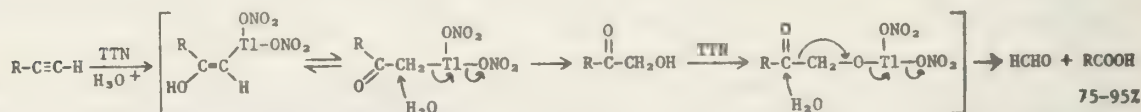


A similar type of reaction is observed with dialkylacetylenes. Unlike benzoin, however, simple dialkyl acyloins show little tendency to enolize under acidic conditions, and hence the product is the acyloin.



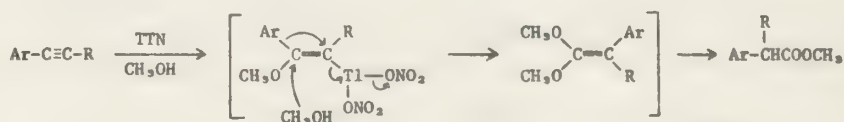
Terminal acetylenes are found to react exothermically with TTN; 2 equiv. of TTN are required for completion of reaction and the products obtained are formaldehyde and carboxylic acids containing one carbon atom less than the starting acetylene (Scheme XII).

Scheme XII



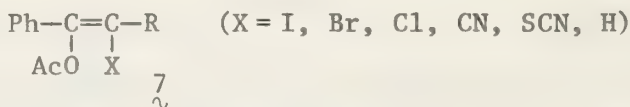
Alkylarylacetylenes react with TTN in aqueous acid to give a complex mixture of products, but when methanol is employed as solvent, smooth oxidative rearrangement occurs, and methyl α -alkylarylacetates are formed in excellent yield (Scheme XIII).

Scheme XIII



In this case, the intermediate oxythallation adduct cannot ketonize, and displacement of the thallium substituent proceeds with concomitant 1,2-aryl migration.

Alkylarylacetylenes have been reported to form stable acetoxythallation adducts by Uemura *et al.*²⁸ Subsequent proto-, halogeno-, cyano-, and thio-cyanodethallation were conducted by reaction with the corresponding Cu(II) or Cu(I) salts in acetonitrile to give a number of olefinic products of the type 7.



BIBLIOGRAPHY

- (a) W. Kitching, *Organometallic Chem. Rev.*, **3**, 61 (1968); (b) For a general review of thallium in organic synthesis, see A. McKillop, and E. C. Taylor, *Advances Organometal. Chem.*, **11**, 147 (1973).
- W. Kruse and T. M. Bednarski, *J. Org. Chem.*, **36**, 1154 (1971).
- (a) U.S. Patent 3452047 (1969); (b) J. E. Byrd, Z. Cassar, P. E. Eaton, and J. Halpern, *J. Chem. Soc. Chem. Commun.*, **40** (1971).
- (a) A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *Tetrahedron Lett.*, 5275 (1970); (b) A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3635 (1973).
- P. K. Grant, H. T. L. Lian, and K. Low, *Austral. J. Chem.*, **28**, 903 (1975).
- (a) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971); (b) E. J. Corey and B. S. Snider, *J. Org. Chem.*, **39**, 256 (1974); (c)

- W. Holick, E. F. Jenny, and K. Heusler, *Tetrahedron Lett.*, 3421 (1975).
7. (a) A. Lethbridge, R. O. C. Norman, C. B. Thomas, and W. J. E. Parr, *J. Chem. Soc. Perkin I*, 231 (1975); (b) A. Lethbridge, R. O. C. Norman, and C. B. Thomas, *ibid.*, 2465 (1975); (c) T. Sasaki, K. Kanematsu, A. Kondo, and K. Okada, *J. Org. Chem.*, 41, 2231 (1976).
 8. E. C. Taylor, C. Chiang, A. McKillop, and J. F. White, *J. Am. Chem. Soc.*, 98, 6750 (1976).
 9. V. G. Aranda, J. Barluenga, and F. Aznar, *Synthesis*, 504 (1974).
 10. (a) S. Uemura, K. Zushi, A. Tabata, A. Toshimitsu, and M. Okano, *Bull. Chem. Soc. Japan*, 47, 920 (1974); (b) S. Uemura, A. Toshimitsu, M. Okano, and K. Ichikawa, *ibid.*, 48, 1925 (1975).
 11. H. Mitani, T. Ando, and Y. Yukawa, *Chem. Lett.*, 455 (1973).
 12. (a) C. Beaudry and M. Zador, *J. Organometal. Chem.*, 102, 265 (1975); (b) S. Uemura, A. Toshimitsu, and M. Okano, *Bull. Chem. Soc. Japan*, 49, 2762 (1976).
 13. (a) S. Uemura, R. Kito, and K. Ichikawa, *Nippon Kagaku Zasshi*, 87, 986 (1966); (b) *Chem. Abstr.*, 65, 19662 (1966).
 14. W. D. Ollis, K. L. Ormand, and I. O. Sutherland, *J. Chem. Soc. C*, 119, (1970).
 15. W. D. Ollis, K. L. Ormand, B. T. Redman, R. D. Roberts, and I. O. Sutherland, *ibid.*, 125 (1970).
 16. L. Farkas, A. Gottsegen, M. Nögrádi, and S. Antus, *J. Chem. Soc. Chem. Commun.*, 825 (1972).
 17. (a) L. Farkas, A. Gottsegen, M. Nögrádi, and S. Antus, *J. Chem. Soc. Perkin I*, 305 (1974); (b) S. Antus, L. Farkas, A. Gottsegen, Z. Kardos Baloh, and M. Nögrádi, *Chem. Ber.*, 109, 3811 (1976); (c) L. Farkas and A. Wolfner, *Acta Chim. Acad. Sci. Hung.*, 88, 175 (1976).
 18. E. C. Taylor, R. L. Robey, K. Liu, B. Favre, A. T. Bozimo, R. A. Conley, C. Chiang, A. McKillop, and M. Ford, *J. Am. Chem. Soc.*, 98, 3037 (1976).
 19. (a) A. McKillop, B. P. Swann, E. Bigham, and E. C. Taylor, *Tetrahedron Lett.*, 5281 (1970); (b) A. McKillop, B. P. Swann, M. Ford, and E. C. Taylor, *J. Am. Chem. Soc.*, 95, 3641 (1973).
 20. (a) J. S. Littler, *J. Chem. Soc.*, 827 (1962); (b) K. B. Wiberg and W. Koch, *Tetrahedron Lett.*, 1799 (1966).
 21. A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Org. Chem.*, 37, 3381 (1972).
 22. A. Romeo and G. Artar, *Tetrahedron*, 28, 5337 (1972).
 23. (a) A. McKillop, B. P. Swann, and E. C. Taylor, *J. Am. Chem. Soc.*, 95, 3340 (1973); (b) *Chem. Abstr.*, 86, 55167r (1977).
 24. G. W. Kenner, K. M. Smith, and J. F. Unsworth, *J. Chem. Soc. Chem. Commun.*, 43 (1973).
 25. M. E. Kuehne and T. J. Giacobbe, *J. Org. Chem.*, 33, 3359 (1968).
 26. (a) A. McKillop, O. Oldenzien, B. Swann, E. C. Taylor, and R. Robey, *J. Am. Chem. Soc.*, 93, 7331 (1971); (b) *ibid.*, 95, 1296 (1973).
 27. S. Uemura, R. Kitoh, F. Fujita, and K. Ichikawa, *Bull. Chem. Soc. Japan*, 40, 1499 (1967).
 28. S. Uemura, H. Tara, M. Okano, and K. Ichikawa, *Bull. Chem. Soc. Japan*, 47, 2663 (1974).

ORGANIC SEMINAR ABSTRACTS

1977-78

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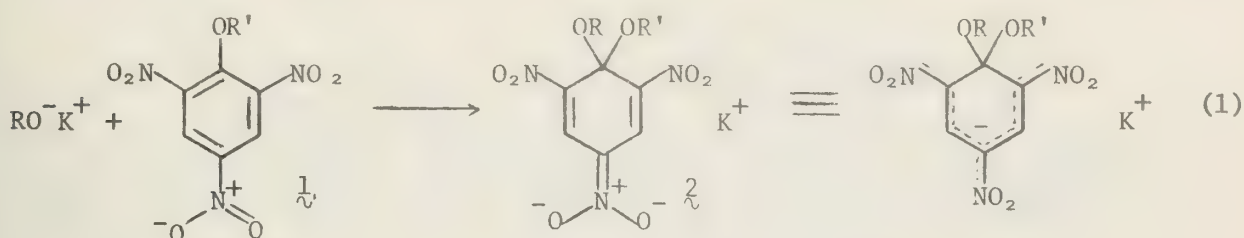
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SYNTHESES OF HETEROCYCLIC RING SYSTEMS THROUGH META-BRIDGING

Reported by Asok Kumar Pal

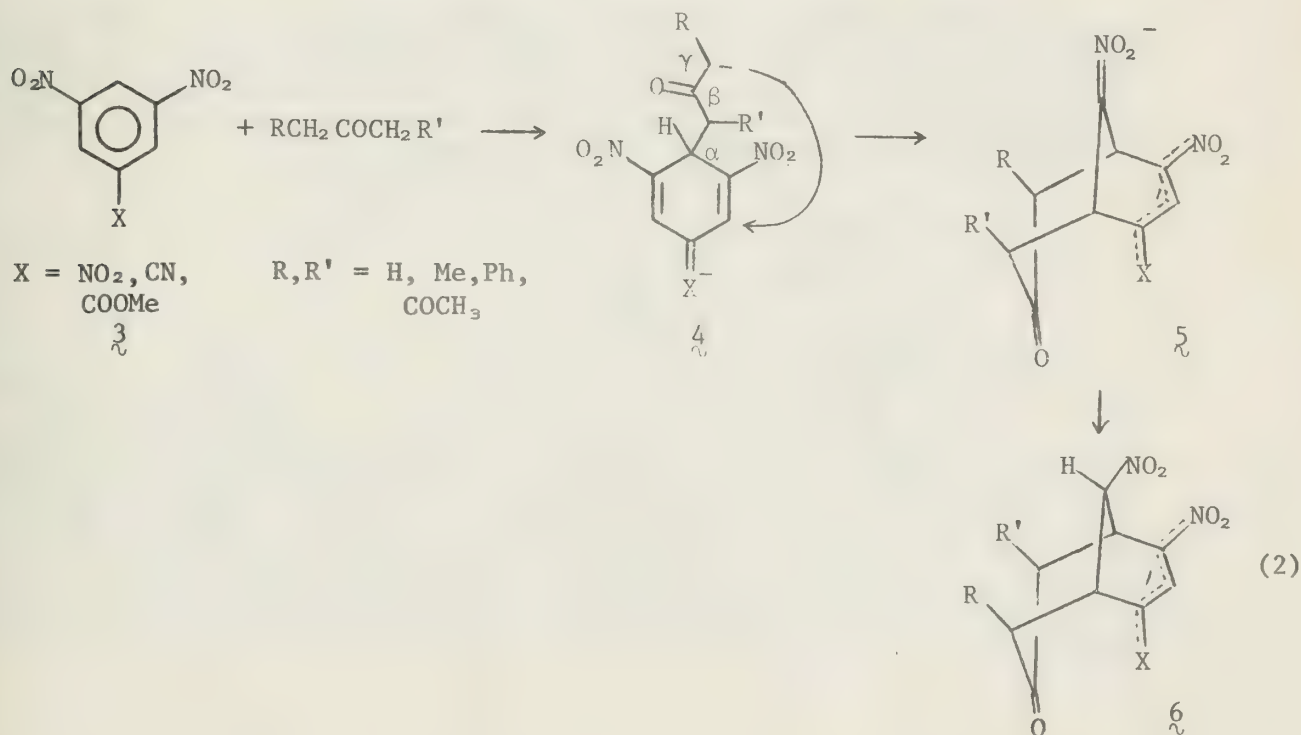
September 15, 1977

When an electron-deficient aromatic compound, e.g. polynitrobenzene or polynitropyridine, is mixed with a nucleophile, the electron density originally associated with the nucleophile is delocalized into the electron-deficient aromatic ring with the concomitant formation of a covalent bond to the aromatic ring, thus forming an anionic σ -complex¹ (Meisenheimer complex) as represented by the Eq. 1:

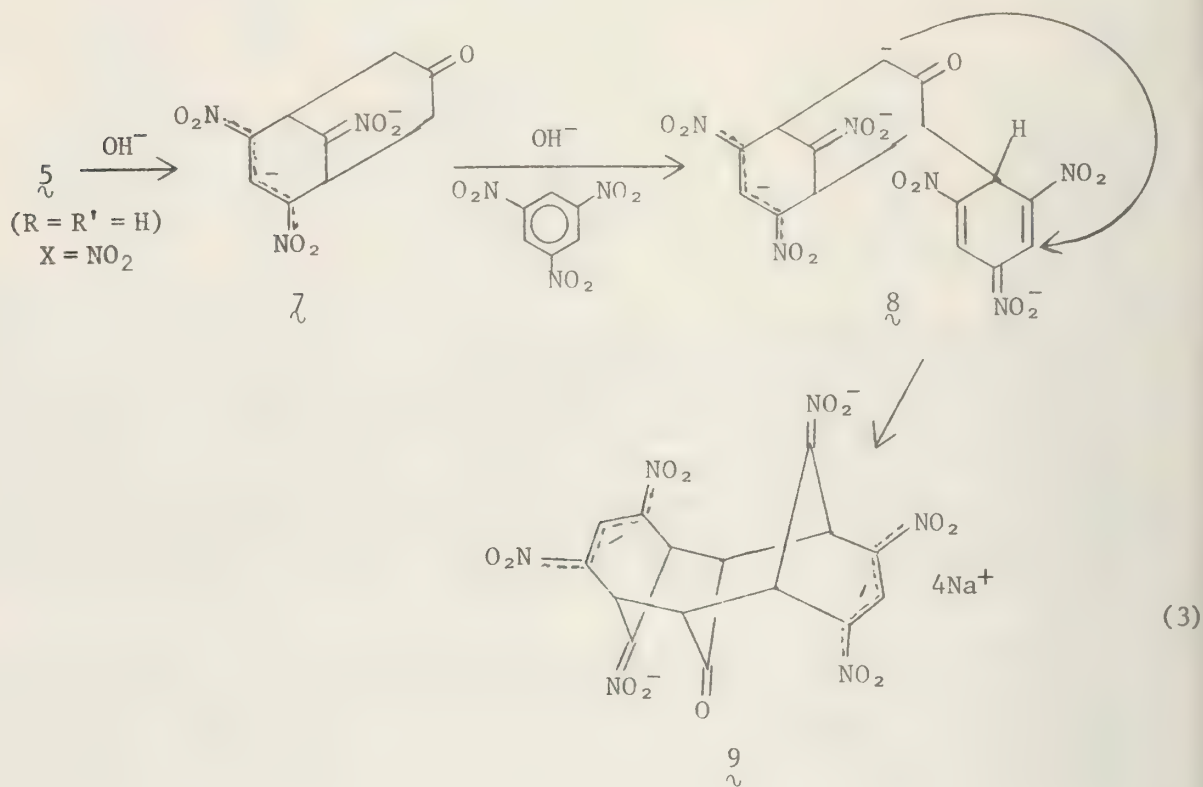


Numerous aromatic and heteroaromatic compounds are now known to form quite stable complexes with many different nucleophiles and the presence of a nitro group is not always essential. Included among the aromatics² are thiophenes, selenophanes, furans, purines, anthracenes, pyridines, diazines, polycyanobenzenes, benzofuroxanes, azulenes, and tropones in addition to benzoid and naphthalenoid polynitroaromatics. The nucleophiles include hydride, sulfite, methoxide, cyanide, hydroxide ions, etc., as well as carbanions, amines, halomethyl anions, and a variety of organometallic compounds.

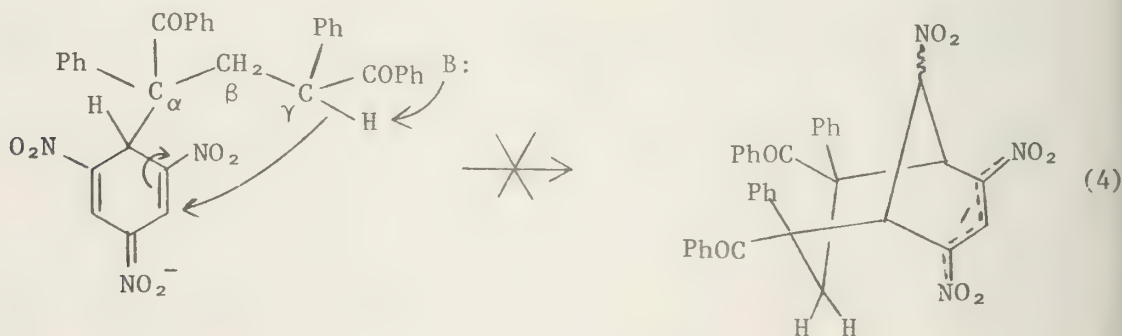
The complexity of the simple addition process (Eq. 1) is greatly increased if there is more than one available site on the ring and/or if the nucleophile is ambident.³ Strauss and others have observed in several cases an intramolecular analog^{4a-g} of the multiple addition to 1-substituted-3,5-dinitrobenzenes (Eq. 2). The mechanism and kinetics have been extensively studied.^{4h-k}

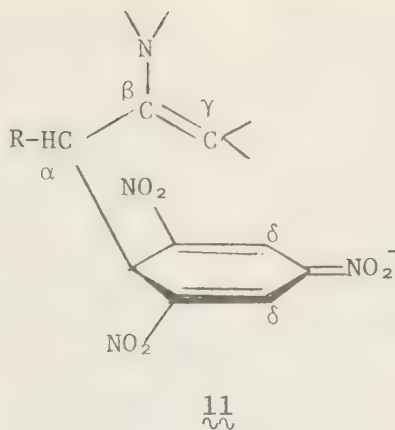
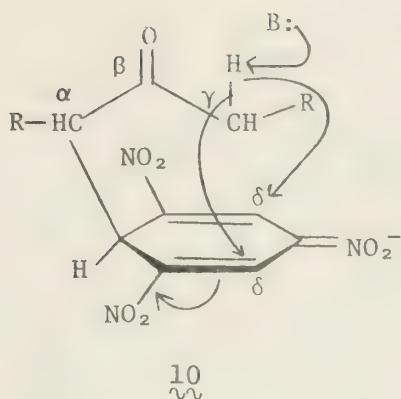


Cyclization of the anionic σ -complex intermediate, e.g. **4**, results from nucleophilic addition if a potential nucleophilic site γ to the tetrahedral ring carbon is available. This reaction is commonly known as "meta-bridging." Abstraction of a proton at C_γ is facilitated either by the presence of a strong base or by the presence of R groups (e.g. phenyl, ester, etc.) capable of stabilizing a carbanion. In strong base and with simple ketones, like acetone, even further addition and cyclization can occur to yield a tetracyclic^{4b} salt like **9** (Eq. 3).

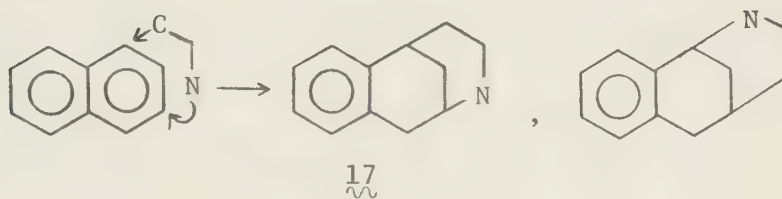
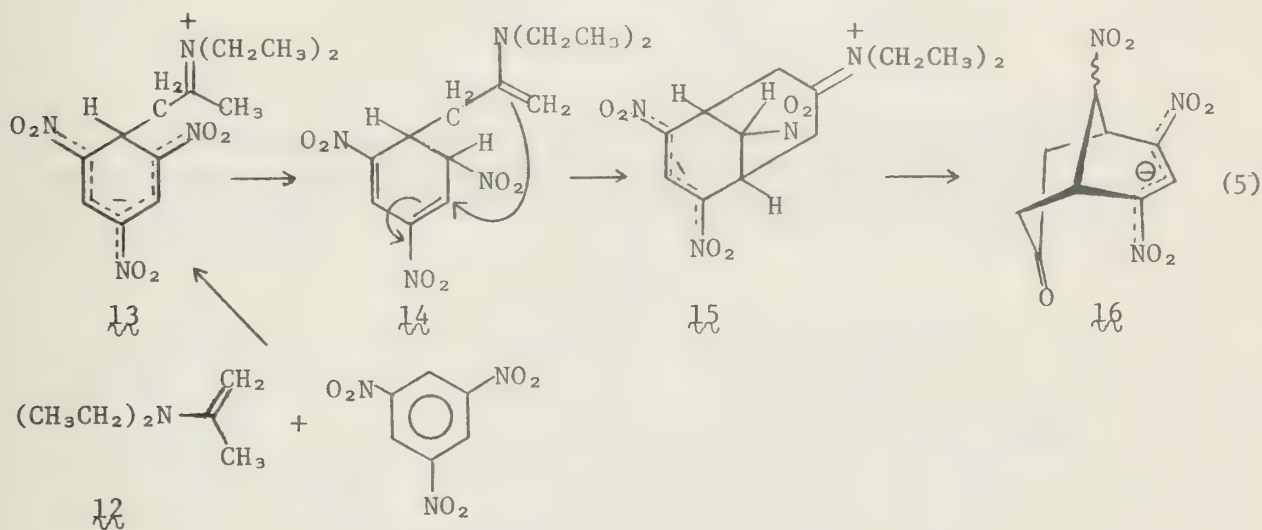


It appears that the σ -complex precursor, **10**, to the bicyclic products always has an sp^2 center adjacent to the nucleophilic site in the side chain and β - to the ring. All attempts to employ such a sequence with potential dicarbanions in which the two nucleophilic sites were not flanking a single carbonyl carbon have failed.² (See Eq. 4.)

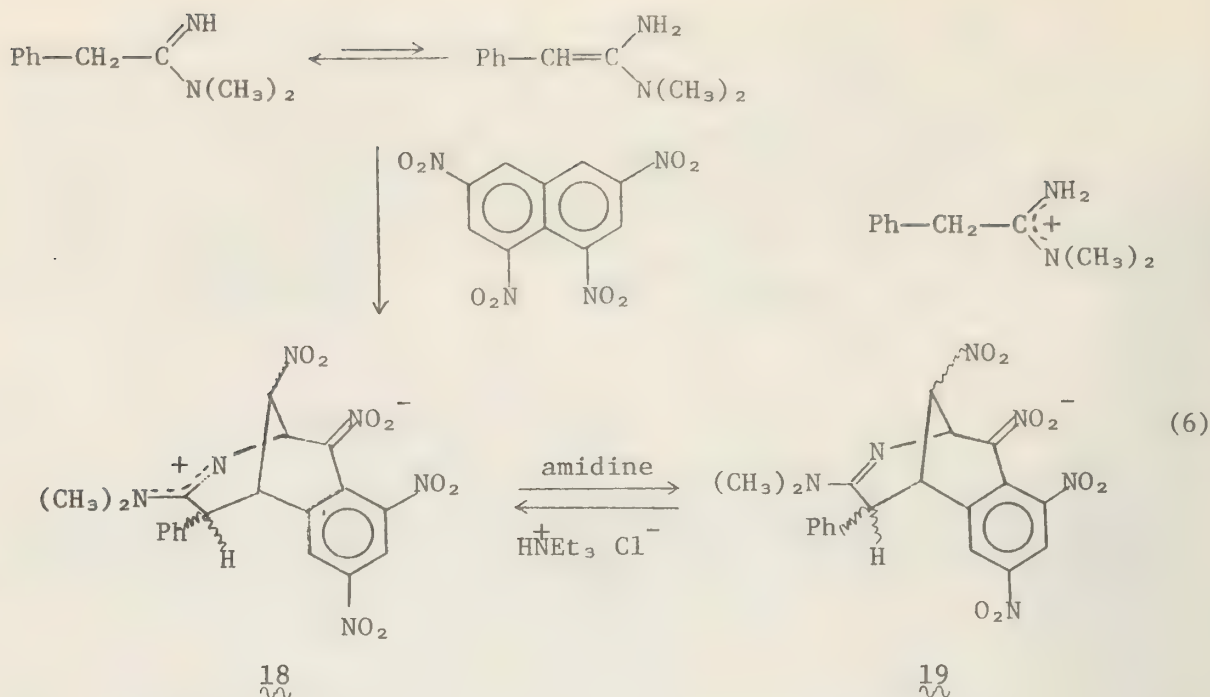




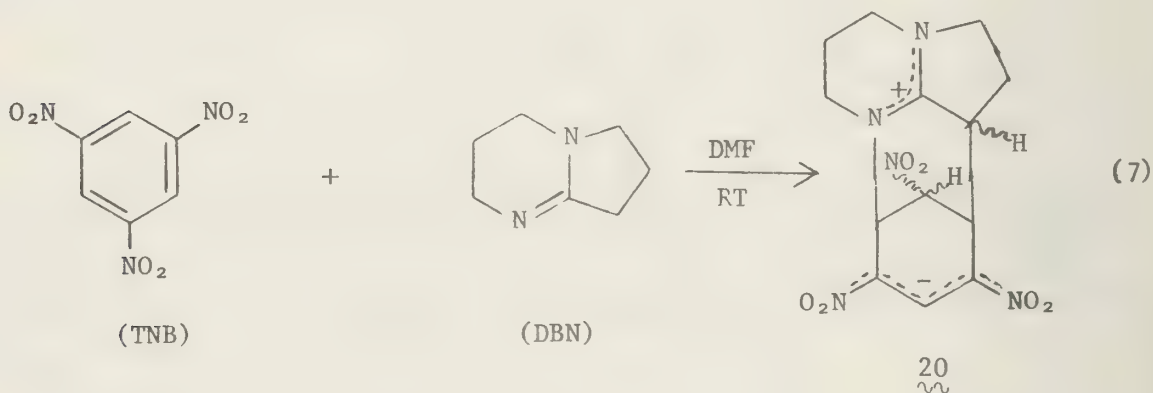
A system similar to 10 is achieved in the case of enamine addition product 11. The enamine carbon C_γ and the electrophilic ring carbon C_δ in the intermediate adduct, 11, are in close proximity and cyclization can readily occur to yield the carbocyclic (3.3.1) system ^{4a,6} (Eq. 5).



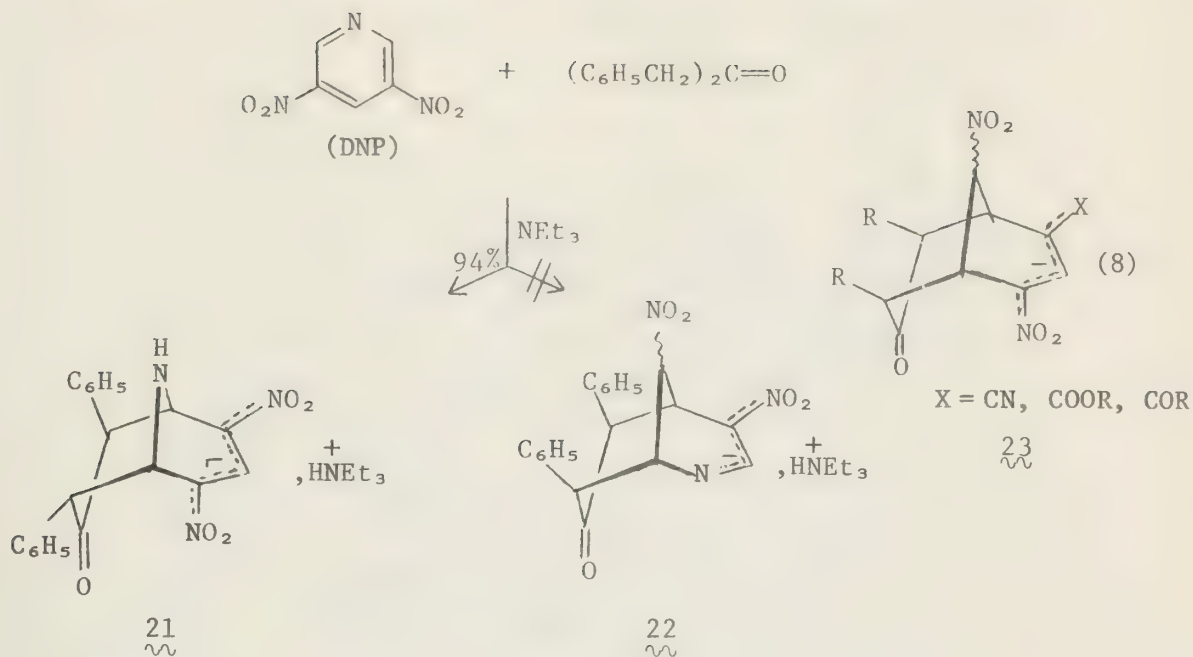
Substitution of a heteroatom for C_γ can provide a useful new way to synthesize bicyclic heterocyclic structures such as the 6,7-benzomorphane skeleton 17. Amidines can be envisioned as a potentially effective meta-bridging function. Strauss, et al.^{7a,b} reported the synthesis of 1,5-methano-3-benzazocines (6,7-benzomorphans) by reaction of α -phenyl-, and α -phenoxy-N,N-dimethylacetamide with polynitronaphthalenes (Eq. 6). Several of these 6,7-benzomorphans have been found to be potentially useful narcotic antagonists.⁸



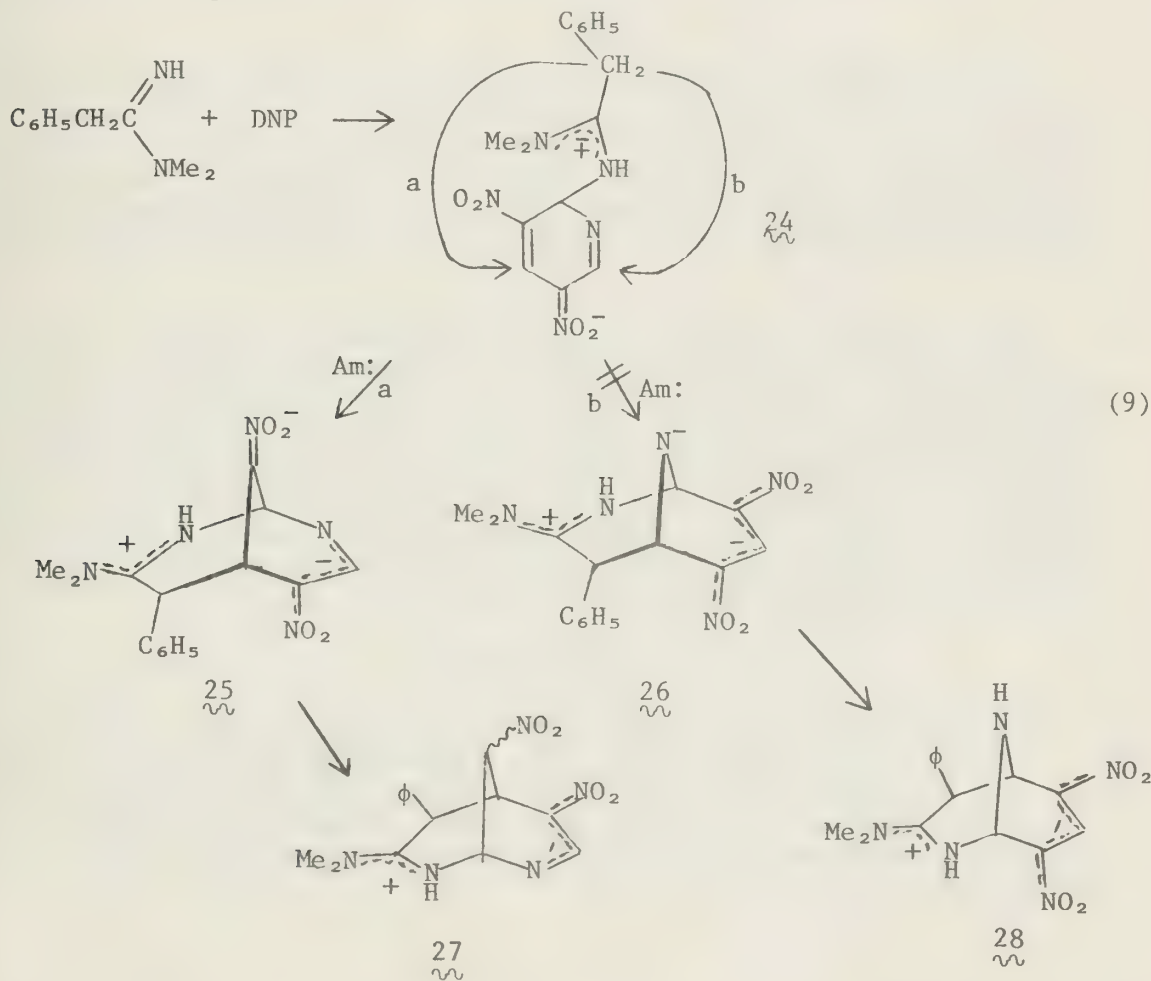
It has also been reported that the meta-bridging reaction of the powerful base 1,5-diazobicyclo(4,3,0)-nonene-5 (DBN) with an equimolar amount of sym-trinitrobenzene (TNB) in dry DMF at room temperature produced 20 in 89% yield (Eq. 7).⁹



Electron-deficient pyridines also form anionic σ -complexes.^{1d-e,10} Reaction of 3,5-dinitropyridine (DNP) with dibenzyl ketone and triethylamine gave 21 in 94% yield.¹¹ There was no evidence for the formation of compound 22 in which the pyridine ring N was involved in bearing the negative charge (Eq. 8). This is in contrast with the finding that all of the bridged 1-X-substituted-3,5-dinitrobenzenes (X being less electron withdrawing than nitro group) yielded ions like 23 in which the X function was active in the delocalization of the negative charge.²



Mixing equivalent amounts of DNP and α -phenoxy- or α -phenylacetamidine in ethyl alcohol results in an orange solution¹¹ due to formation of bicyclic compound 25. However, spectral data indicates that 26 is not formed at all (Eq. 9).





25



26

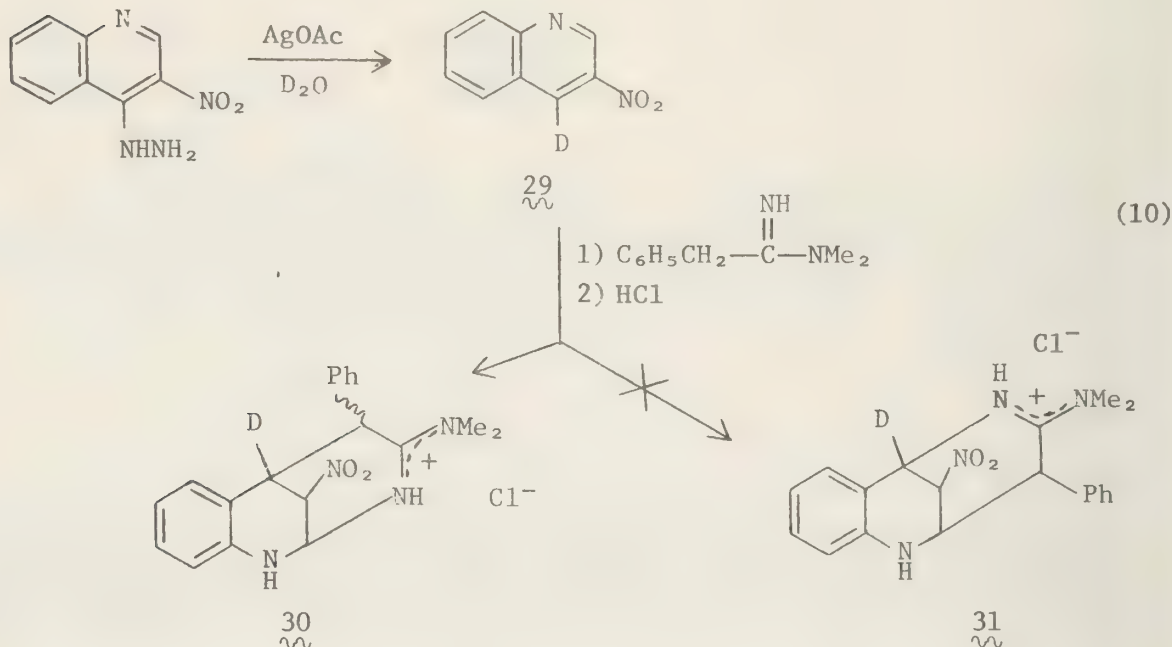


27



28

In another instance, reaction of 29 with α -phenyl-N,N-dimethylacetamidine yielded only 30 and not 31, as evidenced by ^1H nmr spectra, elemental analysis, and comparative spectral data with naphthalene and pyridine adducts.^{7b} (See Eq. 10.)



The explanation for the formation of 30 and not of 31 or of 25 and not of 26 lies in the fact that the amidine attacks the electron-deficient ring at C_2 via N and the intermediate complex expected is thus 24. The mode of cyclization in unsymmetrical complexes such as 24, is controlled by the ability of the ortho substituent (NO_2 or $=\text{N}-$ in 24) to accommodate the accumulating negative charge in the transition state for the cyclization step.

It is evident that meta-bridging reactions of anionic σ -complexes can be useful in preparing heterocyclic ring systems in a one-step process. As an example, the one-step synthesis of the 6,7-benzomorphan ring system is significantly advantageous when compared with the several steps usually required to synthesize such compounds by other methods.¹² Methods may possibly be developed for use with other types of potential "bis" bases, perhaps containing C-C-S, C-C-O, or N-C-S, etc. Several of the bicyclic naphthalene-amidine adducts have been shown to have analgesic and analgesic-antagonist activity.

BIBLIOGRAPHY

- (a) J. Meisenheimer, *Justus Liebigs Ann. Chem.*, **323**, 205 (1902);
 - (b) E. Buncl and J. G. K. Webb, *Tetrahedron Lett.*, 4417 (1976);
 - (c) R. Schaal, F. Terrier, J.-C. Halle, and A.-P. Chatrousse, *ibid.*, 1393 (1970); (d) G. Illuminatti and F. Stegel, *ibid.*, 4169 (1968).
- For lead references, please see: M. J. Strauss, *Acc. Chem. Res.*, **7**, 181 (1974).

3. C. A. Fyfe, M. I. Foreman, and R. Foster, *Tetrahedron Lett.*, 1521 (1969).
4. (a) M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Connor, *J. Org. Chem.*, 35, 383 (1970); (b) K. Kohashi, Y. Ohkura, and T. Momose, *Chem. Pharm. Bull.*, 19, 213 (1971); (c) T. Kabeya, K. Kohashi, Y. Ohkura, and T. Momose, *ibid.*, 19, 645 (1971); (d) K. Kohashi, Y. Ohkura, and T. Momose, *ibid.*, 18, 2151 (1970); (e) T. Momose, Y. Ohkura, and K. Kohashi, *ibid.*, 17, 858 (1969); (f) M. J. Strauss and H. Schran, *Tetrahedron Lett.*, 2349 (1971); (g) I. Kolb, V. Machacek, and V. Sterba, *Coll. Czech. Chem. Commun.*, 41, 1914 (1976); (h) M. J. Strauss, H. F. Schran, and R. R. Bard, *J. Org. Chem.*, 38, 3394 (1973); (i) M. J. Strauss and P. B. Taylor, *ibid.*, 38, 1330 (1973); (j) M. J. Strauss and P. B. Taylor, *ibid.*, 38, 856 (1973); (k) M. J. Strauss and P. B. Taylor, *ibid.*, 37, 3658 (1972).
5. M. Hamana, H. Noda, K. Narimatsu, and I. Ueda, *Chem. Pharm. Bull.*, 23, 2918 (1975).
6. H. Schran and M. J. Strauss, *J. Org. Chem.*, 36, 856 (1971).
7. (a) R. R. Bard and M. J. Strauss, *J. Am. Chem. Soc.*, 97, 3789 (1975); (b) R. R. Bard and M. J. Strauss, *J. Org. Chem.*, 41, 2421 (1976).
8. M. C. Braude, L. S. Harris, E. L. May, J. P. Smith, and J. E. Villerrel, *Adv. Biochem. Psychopharmacol.*, 8, 1 (1973).
9. D. C. Palmer and M. J. Strauss, *Tetrahedron Lett.*, 1431 (1976).
10. (a) M. J. Strauss, *Chem. Rev.*, 70, 667 (1970); (b) F. Terrier, A. P. Chatrousse, and R. Schaal, *J. Org. Chem.*, 37, 3010 (1972).
11. R. Bard and M. J. Strauss, *J. Org. Chem.*, 42, 2589 (1977).
12. K. Kanematsu, R. T. Parfitt, A. E. Jacobson, J. H. Ager, and E. L. May, *J. Am. Chem. Soc.*, 90, 1064 (1968).

RESOLUTION OF STEREOISOMERS BY GAS CHROMATOGRAPHY

Reported by Michael Cheng

September 22, 1977

The resolution of enantiomers is one of the most difficult operations in organic chemistry. Yet, in spite of the great importance of this operation, little progress has been made until recently in the techniques used; the procedure introduced by Pasteur a century ago is in fact still predominantly employed. With the advent of gas-liquid chromatography and the reasoning that gas-liquid chromatography is generally a far more efficient separation technique than other separation methods, resolution of optical isomers has been under intense investigation since 1961. Resolution by gas-liquid chromatography may be effected in two approaches: (a) conversion of the enantiomers into diastereoisomers by a suitable asymmetric reagent followed by chromatography on an optically inactive phase, and (b) resolution of enantiomers on an optically active stationary phase.

Separation of Diastereoisomers on Optically Inactive Phases. In 1961, Casanova and Corey¹ reported the separation of camphor by gas-liquid chromatography of the ketal formed with 2,3-butanediol. Since then, separation of diastereoisomeric alkanes,² alkenes,³ alcohols,^{4,5} esters,^{6,7,8} halides,^{9,10} carbohydrates,¹¹ and amines¹² has been accomplished by gas chromatography on optically inactive phases. Most attention has been paid to amino acid derivatives^{6,13,14,15} because of their biological significance.

In addition to separability, the diastereoisomers employed in gas chromatography must also satisfy certain other conditions. These are (1) easy and quantitative formation with either conservation or complete inversion of configuration of the enantiomers from which they are derived; (2) thermal stability, including absence of racemization during chromatography, which will usually involve relatively high temperature (100 - 200°C); and finally (3) for preparative purposes, reconversion of the diastereoisomers in high yield into the constituting enantiomeric moieties.

It should be realized that chromatography on an optically inactive phase cannot differentiate between enantiomers. Hence, when a mixture of diastereoisomers is separated, each peak may still correspond to two compounds, i.e., the SR and RS, or the SS and RR pairs of enantiomers. Only if the reagent used for derivative formation is optically pure, does each peak correspond to a single compound.

In order to facilitate the selection of stationary phases, optically active resolving reagents (for the formation of diastereoisomers), and gas chromatographic operational variables for the separation of specific diastereoisomers, an understanding of the mechanism of separation is imperative. Different mechanisms for the separation of different classes of compounds were proposed. Most of the compounds have higher resolution factors* on highly polar than on non-polar phases, and the simplifying assumption was therefore made that only solute-solvent[†] interaction of a

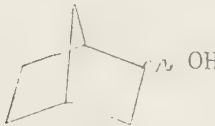

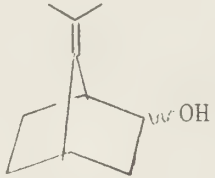
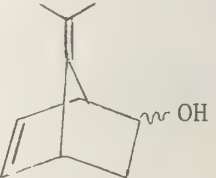
*Resolution factor: Ratio of retention volumes for the more retained compound and the less retained compound

†Solute: The compounds to be separated.
Solvent: The stationary phases.

polar nature need be considered.¹⁶ However, the observation that diastereoisomeric hydrocarbons can be separated on a non-polar phase (e.g., 2,3,4-trimethylhexane on squalane), demonstrates that polar interactions are not uniquely responsible for separation of diastereoisomers.

The first mechanism is specific for compounds containing hydroxyl groups and is based on the fact that intramolecular hydrogen bonds lower the potential of a molecule to form hydrogen bonds with a polar stationary phase. Thus, for a pair of diastereoisomers, the isomer with the higher degree of intramolecular hydrogen bonding will have the lower retention volume on a polar phase. This mechanism should be applicable to other compounds capable of forming hydrogen bonds. An example of this mechanism was reported by DePuy and Story¹⁷ as they chromatographed these four pairs of compounds on a 12 ft by 1/4 inch column packed with 23% by weight Ucon No. 50HB2000 on Celite. I and II were chromatographed at 160°C and 30 ml/min of helium flow; III and IV at 210°C and 41 ml/min helium. The numbers in Figure 1 are retention time in minutes. Another example of

Figure 1

				
	<u>I</u>	<u>II</u>	<u>III</u>	<u>IV</u>
<u>ENDO</u>	104	79	38	30
<u>EXO</u>	96	94	28	33

this mechanism is the behavior of 1,2-cyclopentanediol. Infrared spectroscopy has shown that only the cis isomer is capable of forming an intramolecular hydrogen bond.¹⁸ Nurok and coworkers¹⁹ chromatographed 1,2-cyclopentanediol on sorbitol, an excellent phase for demonstrating hydrogen bonding effects, and obtained the very high resolution factor of 2.65 at 145°C. As expected, the trans isomer has the higher retention volume. This mechanism also applies to acyclic diastereoisomers, e.g., the series of compounds RCHMeCHOHR' studied by Gault and Felkin.⁴ When R is vinyl, isopropenyl or phenyl, infrared studies indicate that there is intramolecular hydrogen bonding, with the threo isomer having the larger population of molecules in the hydrogen bonded form. This observation is explained in Figure 2, which shows that the chelated threo isomer would be expected to be more stable, as the methyl and the R group are eclipsed with hydrogen rather than with each other.

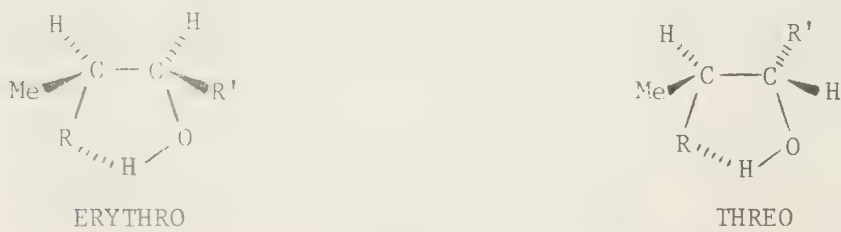


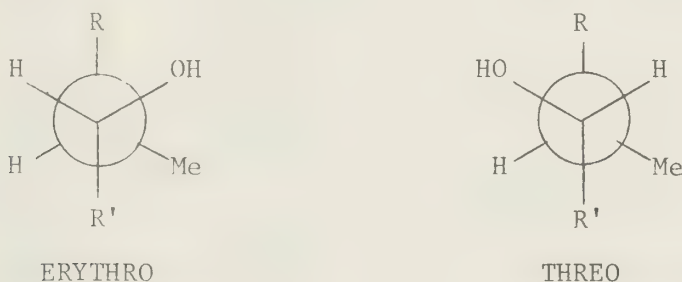
Figure 2

For compounds where there is no intramolecular hydrogen bonding, either because R in Figure 2 is saturated or because the center of unsaturation is distant from the hydroxyl group, the order of elution is opposite to that discussed above, namely, the erythro before the threo, and a different mechanism applies which is discussed later.

The next mechanism also proposed by Nurok and coworkers¹⁹ is based on the fact that two adjacent and aligned dipoles experience a mutual repulsion, the strength of which depends upon the dielectric constant of the medium. Thus, when a molecule having syn dipolar groups is dissolved in a polar solvent, stabilization of the aligned dipoles will occur. For diastereoisomers, e.g., the 2,3-dihalobutanes, Nurok and coworkers considered that the threo isomers of these 2,3-dihalobutanes are likely to have more of the conformation with syn-oriented dipolar groups. Therefore, the threo isomers are stabilized more in the polar stationary phase, and thus have higher retention volume than the erythro isomers.

The third and the most intensely investigated mechanism is based on the fact that the steric requirement of a functional group influences the degree to which it can interact with the stationary phase. An example of this mechanism is afforded by compounds of formula $RCHMeCHOHR'$ where R is saturated or the center of unsaturation is sufficiently distant from the hydroxyl group that no intramolecular hydrogen bonding can occur. The order of elution of these diastereoisomers is opposite to that of the Δ^3 -unsaturated alcohols discussed before. The observed order of elution can be explained on the basis of the differential screening of the hydroxyl group, as illustrated in Figure 3, which shows the most stable conformation for these isomers with the bulky R and R' transoid to each other.

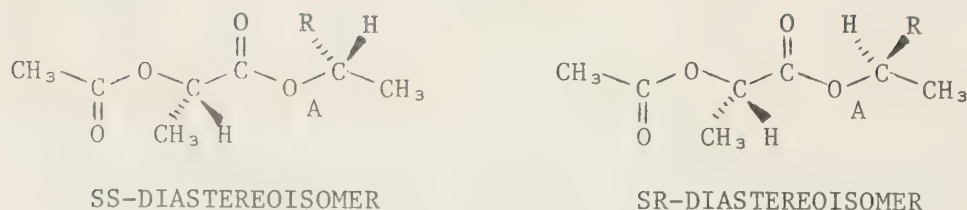
Figure 3



The hydroxyl of the threo isomer is flanked by R and hydrogen; therefore it is more accessible for intermolecular hydrogen bonding with the polar stationary phase as compared to the erythro isomer, whose hydroxyl group is flanked by R and methyl; thus, the threo isomer has higher retention volume.

Karger and coworkers^{8,20,21} have also used differential accessibility of a key polar group to account for the chromatographic behavior of diastereoisomers. The first of the compounds they considered are the α -acetoxypropionates, for which they assumed the "preferred" conformation shown in Figure 4.

Figure 4



The selection of these "preferred" conformations is somewhat arbitrary and the justification for the choice resides in the consistency of the model with experimental results, and it is difficult for one to predict chromatographic results based on these assumptions.

In each of the "preferred" conformations the central ester group is in a different steric environment. In the SS form, the two hydrogens are on the same side of the plane formed by the propionate ester linkage; therefore, the polar ester group is more accessible for interaction with polar stationary phase as compared to the SR form, in which the two hydrogens are on the different sides. From these one can therefore predict that the SS form has higher retention volume.

This interpretation of chromatographic behavior can account not only for the correct elution order, but also for the increase in resolution factor with increasing size of R in Figure 4 (See Table 1.).⁸

Table 1

Column	R	Resolution Factor
20% 1,2,3-Tris-(2-cyanoethoxy) propane at 125°C	Ethyl	1.059
	n-Propyl	1.065
	n-Butyl	1.086
	n-Pentyl	1.100
	n-Hexyl	1.107
	Isopropyl	1.089
	t-Butyl	1.107
20% DC 710 Silicone Oil at 125°C	Ethyl	1.016
	n-Propyl	1.027
	n-Butyl	1.047
	n-Pentyl	1.053
	n-Hexyl	1.054
	Isopropyl	1.064
	t-Butyl	1.079

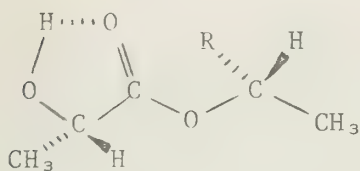
A plausible explanation for the latter observation is that an increase in the bulkiness of R will mean in effect an increase in the population of the suggested stable "preferred" conformer. The separation of α -chloro and α -bromo-alkanoic acids,²¹ and N-trifluoroacetyl alanine²² can also be explained by this hindrance to free rotation.

It is also in accord with the proposed mechanism that the resolution factors drop drastically when the asymmetric centers are removed from the immediate vicinity of the central polar group. Thus, α -acetoxypropionates of primary alcohols 2-methyl and 3-methyl-1-pentanol could not be separated on a packed column,²⁰ and the β -hydroxybutyrate of 3,3-dimethylbutan-2-ol⁸ showed only a shoulder on a column that adequately separated the corresponding α -acetoxypropionates.

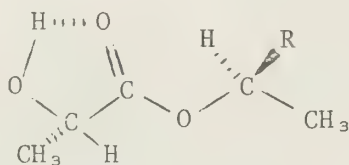
Separation is often greatly enhanced by the incorporation of one or both of the asymmetric carbons into a ring system. In terms of the mechanism discussed in this section, this effect can be explained by the decrease of conformational mobility caused by ring structure, which in turn may increase the population of the "preferred" conformer, thus showing differences in accessibility to the key functional group. Examples are methyl esters of N-trifluoroacetyl-S-prolyl derivatives of amino acids,^{23,24} and N-trifluoroacetyl amino acid esters of (-)-menthol.²⁵ The role of rigidity must not be over-emphasized, however. Nurok²⁶ found that on the polar 1,2,3,4-tetra-(2-cyanoethoxy)-butane stationary phase at 150°C, the α -acetoxypropionate of menthol has a significantly higher resolution factor ($\alpha=1.12$) than that of the more rigid borneol ($\alpha=1.03$). This illustrates that the effect of rigidity may be offset by a relatively low degree of asymmetry in the moiety considered.

The discussion of the influence of ring structure indicates some of the complications due to the simultaneous effect of different structural factors. The lactates of formula $\text{CH}_3\text{CH}(\text{OH})\text{COOCH}(\text{CH}_3)\text{R}$ further illustrate the difficulty of proposing a suitable mechanism. Substitution of a hydroxy group for an acetoxy group does not change the order of elution which is well accounted for by the basic model proposed for the α -acetoxypropionates, modified to include a hydrogen bonded five-membered ring (Figure 5).

Figure 5



SS-DIASTEREOISOMER



SR-DIASTEREOISOMER

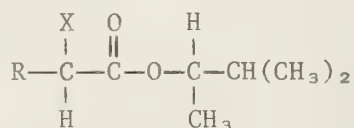
However, in contrast to α -acetoxypropionates, the resolution factor of these lactates decreases with increasing chain length of R. This result is not completely understood at the present time. It may be possible for the straight-chain R group to interact with the hydroxyl group, thus disrupting the intramolecular hydrogen bond, resulting in increased conformational mobility on the acid side of the molecule, therefore decreasing the resolution factor.

The possibility of electronic effects on separation was also investigated by Karger and coworkers.²¹ A series of mandelate esters were chromatographed on 20% ethylene glycol isophthalate packed column, and the results are shown in Table 2.

Table 2

R	σ	α (X = OH)	α (X = OAc)
C ₆ H ₅	-	NS	1.032
p-MeO-C ₆ H ₄	-0.27	NS	NS
m-MeO-C ₆ H ₄	+0.12	1.033	NS
p-F-C ₆ H ₄	+0.06	NS	1.016
p-Cl-C ₆ H ₄	+0.23	1.018	NS
p-Br-C ₆ H ₄	+0.23	1.041	NS
m-Me-C ₆ H ₄	-0.07	NS	NS
p-Me-C ₆ H ₄	-0.17	NS	NS

NS: No Separation



No clear trends are visible for both the α -acetoxy and the α -hydroxy series; however, one can notice the marked effect the substituents at the meta and para position can have on the differential partition behavior of an aromatic diastereoisomeric system.

Karger and coworkers^{22,27} also investigated the separation of amides on packed and open tubular columns. They concluded that primary and secondary amides consistently have higher resolution factors than the corresponding esters, because (1) the hydrogen(s) on the amide nitrogen can interact with the stationary phase through hydrogen bonding, and (2) the rigidity imparted by the partial double bond character of the C-N bond in amide linkage.

Resolution of Enantiomers on an Optically Active Phase. Most of the investigation done under this heading is in the field of amino acids. Gas chromatographic resolution of N-trifluoroacetyl- α -amino acid esters on the optically active phase was first reported in the period 1967-1970.^{28,29,30} Different mechanisms were proposed for different stationary phases; however, these mechanisms are all based on the fact that hydrogen bonding is possible between the stationary phase and the solute.

Gil-Av and coworkers first successfully resolved enantiomeric N-TFA-amino acid esters on optically active N-TFA-L-isoleucine lauryl ester and N-TFA-L-phenylalanine cyclohexyl ester.²⁸ The proposed hydrogen bonded association complex is shown in Figure 6.

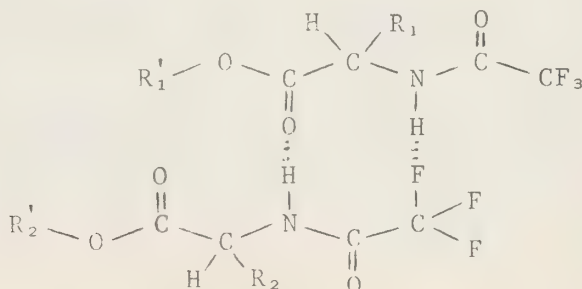
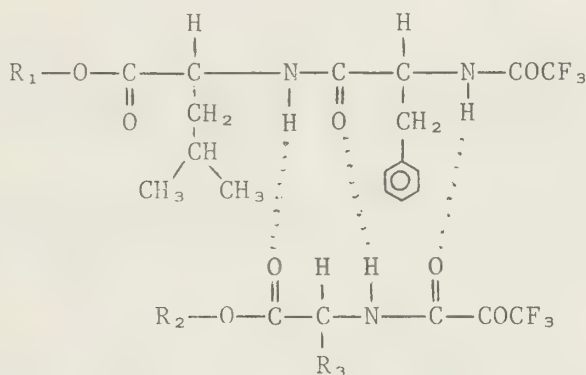


Figure 6

Inspection of models shows that there are certain conformations in which there is more interference between the R groups on the α -carbon atoms for the RS- than for the SS-complex. This is in accord with the lower retention volume for the R isomer on an S-phase and vice versa. The weakness of the NH-F hydrogen bond is the main shortcoming of this model, although this kind of bond is known to be in existence. An alternative form that should be considered is the one containing two $\text{>N-H}\cdots\text{O=C<}$ bonds as discussed next.

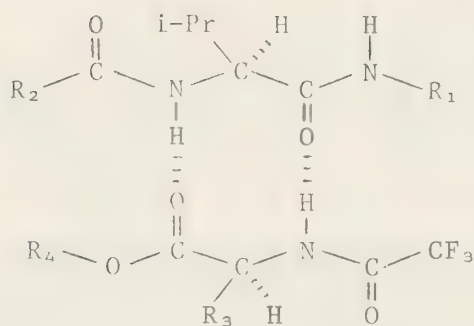
On the dipeptide phase N-TFA-L-phenylalanyl-L-leucine cyclohexyl ester, W. Parr and coworkers³¹ proposed that the high efficiency of the dipeptide phases for the resolution of enantiomeric solutes is due to the formation of a triply hydrogen-bonded complex between the enantiomeric solute and the chiral solvent as shown in Figure 7.

Figure 7

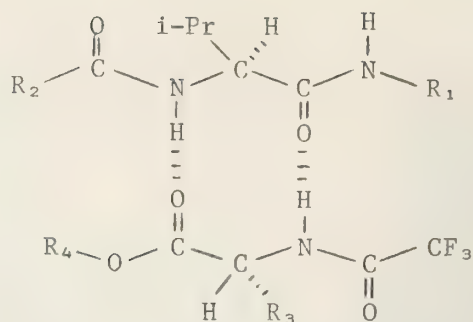


Feibush and Gil-av³⁰ called it a hydrogen-bonded "diastereomeric" association complex, and stated that when such association occurs, a particular conformation is imposed on the solute, with the acceptor and the donor groups forming part of a spiral turn, the handedness of which is determined by the configuration of the amino acids in the stationary phase. In the conformation in which they are hydrogen-bonded to the solvent, the enantiomeric solutes thus cease to be the mirror images of each other and become "conformational" diastereoisomers. Interaction of such "diastereoisomers" with solvent will in general be different. It is also observed that too much bulkiness in the solute-solvent system appears to weaken hydrogen bonding and, thereby, decrease the molar fraction of the association complex in the stationary phase. The shortcoming of this model is that it is required that the C-N bond in the amide function to be cis. However, it was found by NMR measurement that the trans-isomer is the exclusive form for dilute solution of a secondary alkyl amide.³² But, if the hydrogen bonding interaction is favorable enough, the amide linkage may be forced into cis conformation.

The latest mechanism proposed by Beitler and Feibush³³ is shown in Figure 8. This proposed associate was resulted from IR studies made by Mizushima and coworkers^{34,35} who studied the IR spectra of the crystalline structure of different diamides, similar to those shown in Figure 8, with polarized light. They concluded that, for example, N-acetyl-L-leucine methyl amide possesses the crystalline structure of poly-L-alanine,³⁶ which is very similar to this associate between the solute and the stationary



SS-ASSOCIATE



SR-ASSOCIATE

Figure 8

phase. For the SS associate, the isopropyl group of the stationary phase is closer to the R group of the N-TFA amino acid ester; thus, there should be more interaction due to dispersion forces between the pertinent apolar groups than the SR associate. Therefore, the S amino acid should emerge last, as indeed it does. At this point, one can see that the interaction of the R groups is used as a fudge factor; here, a dispersive force is employed, and previously it was used as a repulsive force. Therefore, it is obvious that these mechanisms are only useful in explaining the experimental results.

Gas chromatography is a superior method in the resolution of stereoisomers with which one can resolve the isomers and have the knowledge of absolute configuration of each isomer at the same time, provided the mechanism of resolution is known. This is why knowledge of the mechanism is imperative in the resolution of stereoisomers. The mechanism of resolution is still unknown for some classes of compounds. Therefore, this points to the direction of further investigation.

BIBLIOGRAPHY

1. J. Casanova and E. J. Corey, Chem. Ind. (London), 1664 (1961).
2. M. C. Simmons, D. B. Richardson, and I. Dvovetzky, "Gas Chromatography 1960," ed., R. P. Scott, Butterworth, London, 1960, p. 211.
3. W. E. Doering and W. R. Roth, Tetrahedron, 18, 67 (1962).
4. Y. Gault and H. Felkin, Bull. Soc. Chim. France, 742 (1965).
5. C. L. Arcus, L. A. Cort, T. J. Howard, and L. B. Loc, J. Chem. Soc., 1195 (1960).
6. E. Gil-Av, R. Charles-Sigler, G. Fischer, and D. Nurok, J. Gas Chromatogr., 4, 51 (1966).
7. H. C. Rose, R. L. Stern, and B. L. Karger, Anal. Chem., 38, 496 (1966).
8. B. L. Karger, R. L. Stern, H. C. Rose, and W. Kean, "Gas Chromatography 1966," ed., A. B. Littlewood, Institute of Petroleum, London, 1967, p. 240.
9. R. Stern, E. R. Atkinson, and F. C. Jennings, Chem. Ind., 1785 (1962).
10. H. L. Goering and D. W. Larson, J. Am. Chem. Soc., 81, 5937 (1959).
11. G. E. Pollock and P. A. Jeramany, J. Gas Chromatogr., 6, 413 (1968).
12. B. Halpern and J. W. Westley, Chem. Commun., 34 (1966).
13. F. Weygand, A. Prox, L. Schmidhammer, and W. Koenig, Angew. Chem. Int. Ed. (Eng.), 2, 183 (1963).

14. G. E. Pollock and V. I. Oyama, J. Gas Chromatogr., 4, 126 (1966).
15. B. Halpern and J. W. Westley, Chem. Commun., 246 (1966).
16. C. H. DePuy and P. R. Story, Tetrahedron Lett., 20 (1959).
17. E. Gil-Av and D. Nurok, "Advances in Chromatography", Vol. 10.
18. L. P. Kuhn, J. Am. Chem. Soc., 74, 2492 (1952).
19. D. Nurok, G. L. Taylor, and A. M. Stephen, J. Chem. Soc., 291 (1968B).
20. H. C. Rose, R. L. Stern, and B. L. Karger, Anal. Chem., 38, 496 (1966).
21. R. L. Stern, B. L. Karger, W. Keane, and H. C. Rose, J. Chromatogr., 39, 17 (1969).
22. J. W. Westley, B. Halpern, and B. L. Karger, Anal. Chem., 40, 2046 (1968).
23. J. W. Westley and B. Halpern, "Gas Chromatography 1968", ed., S. L. A. Harbourn, Institute of Petroleum, London, 1969, p. 119.
24. B. Halpern and J. W. Westley, Tetrahedron Lett., 2283 (1966).
25. S. W. Vitt, M. B. Saporovskaya, I. P. Gudkova, and V. M. Belikov, Tetrahedron Lett., 2575 (1965).
26. D. Nurok, Ph.D. Thesis, University of Capetown, 1966.
27. B. L. Karger, S. Herliczek, and R. L. Stern, Chem. Commun., 625 (1969).
28. E. Gil-Av, B. Feibush, and R. Charles-Sigler, "Gas Chromatography 1966", ed., A. B. Littlewood, Institute of Petroleum, London, 1967, p. 227.
29. B. Feibush and E. Gil-Av, Tetrahedron Lett., 3345 (1967).
30. B. Feibush and E. Gil-Av, Tetrahedron, 26, 1361 (1970).
31. W. Parr, C. Yang, E. Bayer, and E. Gil-Av, J. Chromatogr. Sci., 8, 591 (1970).
32. W. E. Stuart and T. H. Siddall, Chem. Rev., 70, 517 (1970).
33. U. Beitler and B. Feibush, J. Chromatogr., 123, 149 (1976).
34. S. Mizushima, T. Shimanouchi, M. Tsuboi, K. Kuratani, T. Sugita, M. Mataga, and R. Souda, J. Am. Chem. Soc., 75, 1863 (1953).
35. T. Moriwaki, M. Tsuboi, T. Shimanouchi, and S. Mizushima, J. Am. Chem. Soc., 81, 5194 (1959).
36. C. H. Bamford, A. Elliot, W. Hanby, and I. Trotter, Nature, 173, 27 (1954).

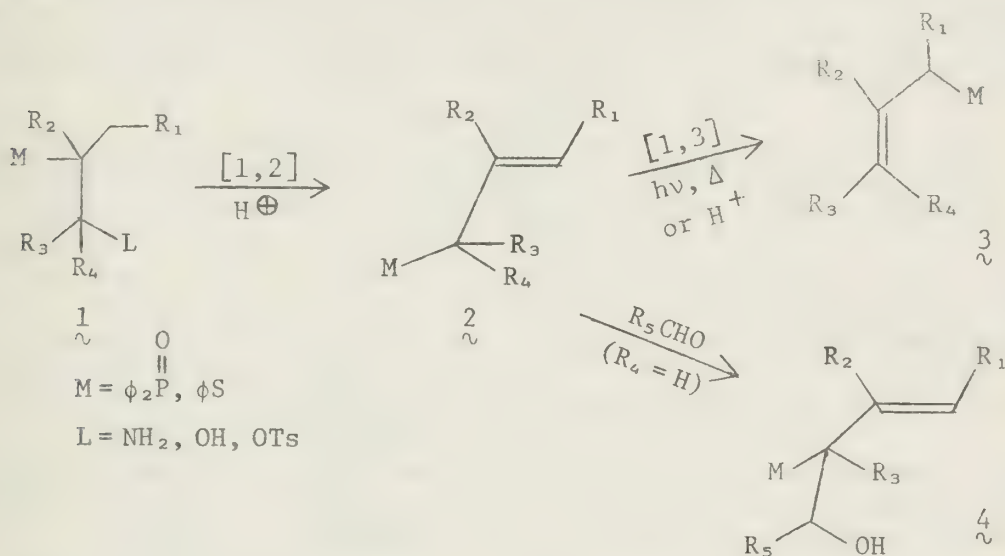
RECENT DEVELOPMENTS IN CATION-INDUCED MIGRATION OF SYNTHETICALLY USEFUL FUNCTIONALITIES

Reported by Christopher K. VanCantfort

September 29, 1977

Experimental results produced since the beginning of this decade have served to shatter two of the oldest and most tenaciously held myths concerning carbonium ion migrations. The concept that the group best able to stabilize a positive charge is the best migrating group¹ has been repeatedly rebuked by studies² demonstrating the preferred migration of electronegative groups. Furthermore, the idea that "migratory aptitude"³ is a quantifiable and genetic property of a group appears wholly untenable.^{2a} Recent interests in migration reactions (*i.e.*, reactions in which the mobile functional group is unchanged in proceeding from origin to terminus) have centered on their potential synthetic utility. Of equal interest is the identification and definition of factors which influence the course of these reactions. Both of these aspects of migration reactions will be explored in this presentation.

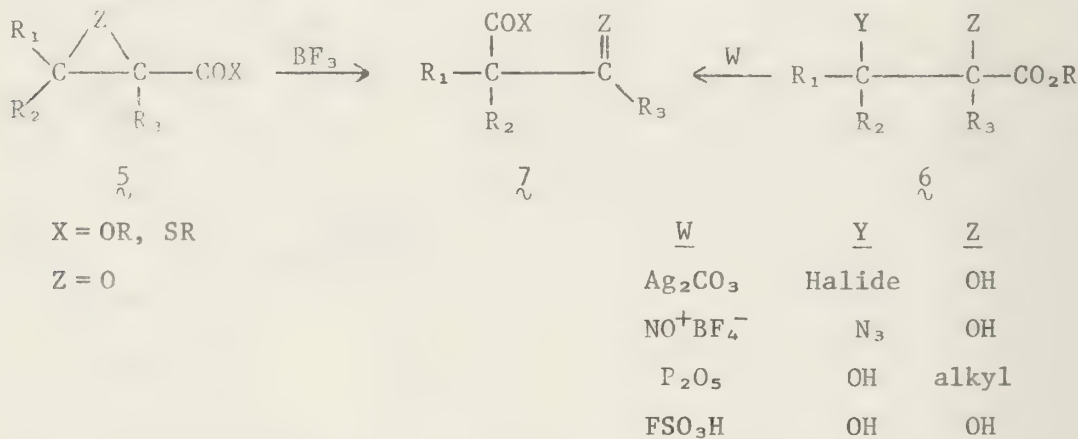
Warren has successfully and extensively exploited the synthetic utility of mobile functional groups based on second row elements⁴ whose migration can readily be induced by α -carbonium ion generation.



The readily accessible phenylthio derivatives (1, $M = \phi S$)⁵ can be rapidly transformed via [1,2] migration to the corresponding allyl phenyl sulfide (2) under mild conditions. Allylic sulfides and sulfoxides (the latter available directly from the former) are known to be extremely useful synthetic intermediates.⁶ Furthermore, the initial migration product (2, $M = \phi S$) can quantitatively undergo a [1,3] thio-allylic rearrangement to yield a new and different allylic sulfide (3).^{5b,c} The mechanism for this [1,3] migration has been investigated.⁷ Kwart has studied extensively the [1,3] thio-allylic rearrangement mechanism and has championed an alternate mode of migration.^{6b} The reaction sequence (1 \rightarrow 3) involves charge affinity inversion ("umpolung") with a net regioselective shift of the functional group one carbon in either direction. The thermodynamically less favorable product can be provoked when appropriate substituents are utilized.^{5a}

The diphenylphosphinoyl analog ($1, M = \phi_2\overset{\text{O}}{\underset{\text{||}}{\text{P}}}$) also readily undergoes a [1,2] migration⁸ to produce regioselectively⁹ and in high yield the E-isomer of the more substituted allylphosphine oxide ($2, M = \phi_2\overset{\text{O}}{\underset{\text{||}}{\text{P}}}$). The reaction has been shown to proceed with stereochemical inversion at the migration terminus and retention of configuration in the migrating group.¹⁰ A mechanism has been postulated in accord with this and other evidence.¹¹ The factors which influence diphenylphosphinoyl migration over alkyl migration have been thoroughly studied.¹² Again, thermodynamically unfavorable products can be generated under appropriate conditions.^{9,13} The scope and limitations of the migration reaction with respect to origin and terminus substitution patterns has been thoroughly analyzed.¹⁴ The migration product ($2, M = \phi_2\overset{\text{O}}{\underset{\text{||}}{\text{P}}}$) can be further utilized via 4 ($M = \phi_2\overset{\text{O}}{\underset{\text{||}}{\text{P}}}$) to stereo- and regioselectively produce dienes.¹⁵ The principle of "umpolung" is once again invoked to construct a molecule entirely from electrophilic addenda.

Although migrations of electronegative groups such as $-\text{COX}$ ($X = \text{H}, \text{R}, \text{OR}, \text{etc.}$) adjacent to potential cationic centers have long been known,¹⁶ only recently have these rearrangements been systematically studied for their synthetic potential. It has been demonstrated that glycidic esters ($5, X = \text{OR}$),^{2a,17} glyceric esters ($6, Y = Z = \text{OH}$),^{18,19} and their corresponding halohydrins ($6, Y = \text{halide}, Z = \text{OH}$)¹⁹ and azidohydrins ($6, Y = \text{N}_3, Z = \text{OH}$)¹⁹ cleanly undergo [1,2] carboalkoxy migrations in high yield for



a variety of substituents under appropriate conditions. Beta-hydroxy esters ($6, Y = \text{OH}, Z = \text{alkyl, aryl, or H}$)²⁰ behave similarly. Evidence for a concerted migration mechanism based on the stereochemistry of substrates and products has been accumulated.^{2a,19,21} The observed rearrangement of the corresponding thiol esters ($5, X = \text{SR}$) has been thoroughly studied.^{2b,21b,22} The latter migration constitutes the first known example of a non-biochemical thiol ester migration and has been invoked to rationalize the biosynthesis of tropic acid²³ and the conversion of succinyl CoA to methylmalonyl CoA.^{21b} Every study cited to date establishes the preferred order of migration to be: $\phi > -\text{COX} > \text{alkyl or H}$. While the latter portion of this order is seldom reversed, the former can be^{20,21b} under appropriate conditions, thereby resulting in carboxyl migration in preference to all other groups. Carboalkoxy groups show the same migration tendency in acid catalyzed dienone-phenol rearrangements where aromatization is a strong driving force.²⁴

BIBLIOGRAPHY

1. C. K. Ingold, "Structure and Mechanism in Organic Chemistry," London, Bell, 1953, p. 476.
2. For leading references see (a) J. Kagan, D. A. Agdeppa, Jr., S. P. Singh, D. A. Meyers, C. Boyajian, C. Poorker, and B. E. Firth, *J. Am. Chem. Soc.*, 98, 4581 (1976); (b) D. J. Dagli, R. A. Gorski, and J. Wemple, *J. Org. Chem.*, 40, 1741 (1975).
3. W. E. Beckmann and F. H. Moser, *J. Am. Chem. Soc.*, 54, 1124 (1932).
4. (a) A. H. Davidson, P. K. G. Hodgson, D. Howells, and S. Warren, *Chem. Ind. (London)*, 455 (1975); (b) P. K. G. Hodgson, R. Shepherd, and S. Warren, *J. Chem. Soc. Chem. Commun.*, 633 (1974); (c) P. Brownbridge, P. K. G. Hodgson, R. Shepherd, and S. Warren, *J. Chem. Soc., Perkin I*, 2024 (1976).
5. (a) P. Brownbridge, I. Fleming, A. Pearce, and S. Warren, *J. Chem. Soc. Chem. Commun.*, 751 (1976); (b) P. Brownbridge and S. Warren, *J. Chem. Soc. Chem. Commun.*, 820 (1975); (c) P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin I*, 1131 (1977).
6. (a) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, 7, 147 (1974); (b) H. Kwart and T. J. George, *J. Am. Chem. Soc.*, 99, 5214 (1977).
7. P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin I*, 2125 (1976).
8. (a) P. F. Cann and S. Warren, *Chem. Commun.*, 1026 (1970); (b) P. F. Cann, D. Howells, and S. Warren, *Chem. Commun.*, 1148 (1971); (c) P. F. Cann, D. Howells, and S. Warren, *J. Chem. Soc., Perkin II*, 304 (1972); (d) D. Howells and S. Warren, *J. Chem. Soc., Perkin II*, 1472 (1973).
9. A. H. Davidson, I. Fleming, J. I. Grayson, A. Pearce, R. L. Snowden, and S. Warren, *J. Chem. Soc., Perkin I*, 550 (1977).
10. F. H. Allen, O. Kennard, L. R. Nassimbeni, R. G. Shepherd, and S. Warren, *Nature*, 248, 670 (1974).
11. F. Allen, O. Kennard, L. Nassimbeni, R. Shepherd, and S. Warren, *J. Chem. Soc., Perkin II*, 1530 (1974).
12. (a) D. Howells and S. Warren, *J. Chem. Soc., Perkin II*, 1645 (1973); (b) D. Howells and S. Warren, *J. Chem. Soc., Perkin II*, 992 (1974).
13. I. Fleming, A. Pearce, and R. L. Snowden, *J. Chem. Soc. Chem. Commun.*, 182 (1976).
14. A. H. Davidson, C. Earnshaw, J. I. Grayson, and S. Warren, *J. Chem. Soc., Perkin I*, 1452 (1977).
15. (a) A. H. Davidson and S. Warren, *J. Chem. Soc. Chem. Commun.*, 148 (1975); (b) A. H. Davidson and S. Warren, *J. Chem. Soc. Chem. Commun.*, 639 (1976); (c) A. H. Davidson and S. Warren, *J. Chem. Soc. Chem. Commun.*, 181 (1976).
16. R. M. Acheson, *Acc. Chem. Res.*, 4, 177 (1971).
17. S. P. Singh and J. Kagan, *J. Am. Chem. Soc.*, 91, 6198 (1969).
18. J. Kagan, D. A. Agdeppa, Jr., and S. P. Singh, *Helv. Chim. Acta*, 55, 2252 (1972).
19. J. Kagan, D. A. Agdeppa, Jr., D. A. Meyers, S. P. Singh, M. J. Walters, and R. D. Wintermute, *J. Org. Chem.*, 41, 2355 (1976).
20. T. H. Phan and H. Dahn, *Helv. Chim. Acta*, 59, 335 (1976).
21. (a) J. M. Domagala, R. D. Bach, and J. Wemple, *J. Am. Chem. Soc.*, 98, 1975 (1976); (b) R. A. Gorski, D. J. Dagli, and J. Wemple, *J. Am. Chem. Soc.*, 98, 4588 (1976).
22. J. Wemple, *J. Am. Chem. Soc.*, 92, 6694 (1970).
23. J. Domagala and J. Wemple, *Tetrahedron Lett.*, 14, 1179 (1973).
24. (a) J. N. Marx, J. C. Argyle, and L. R. Norman, *J. Am. Chem. Soc.*, 96, 2121 (1974); (b) R. M. Acheson and R. F. Flowerday, *J. Chem. Soc., Perkin I*, 2339 (1974); (c) T. Suehiro and S. Yamazaki, *Bull. Chem. Soc. Jap.*, 48, 3655 (1975).

KINETICS AND MECHANISM OF PERMANGANATE OXIDATIONS OF CARBON-CARBON MULTIPLE BONDS IN ACIDIC MEDIA

Reported by Susan Ruth Krauss

October 3, 1977

The oxidation of carbon-carbon multiple bonds by permanganate ion is an important and well-known reaction in organic chemistry.¹ Under acidic aqueous conditions, cleavage products usually predominate, although α,β -dioxo compounds and α -hydroxy ketones are also produced. The mechanism of these reactions is influenced by reaction conditions which determine the stable oxidation states of manganese, as well as possible reactions between manganese species, and by the characteristics of the substrate. Some work has been done on permanganate oxidations in acetic anhydride.²

The majority of these reactions are characterized by the accumulation and decay of a spectrophotometrically observable manganese intermediate. Oxygen-18 tracer experiments indicate exclusive oxygen transfer from permanganate.^{3,4} In the case of trans-cinnamic acid, the average oxidation state of manganese at the time corresponding to maximum concentration of intermediate,⁵ the effect of replacement of the α or β proton with deuterium,⁶ and the effect of substituents on the aromatic nucleus⁷ were determined. Tracer studies with radioactive carbon and hydrogen showed that formic acid formed by the permanganate oxidation of fumaric acid is derived exclusively from one of the methine groups, and that one C-H bond remains intact during the reaction.⁸ The nature of intermediates, product distribution as a function of pH and mole ratio of reactants, and Arrhenius parameters were investigated for numerous reactions.^{9,10,11} Information about the relative importance of electronic and steric factors was also obtained.^{9,10} Orbital symmetry rules were applied to alkene oxidations.¹² Sterically rigid olefins, which did not yield cleavage products, formed uniquely stable intermediates whose decomposition was not observed.¹³

There is general agreement that cyclic manganese esters are formed in the initial step of this reaction. Various other subsequent intermediates have been proposed to account for the kinetic and mechanistic data obtained from reactions of various substrates.

In a related area, it was found that potassium permanganate can be solubilized in benzene by complexing with dicyclohexyl-18-crown-6¹⁴ or by quaternary ammonium salts¹⁵ (phase transfer catalysts) to provide a convenient and efficient oxidant for organic compounds under mild conditions.

BIBLIOGRAPHY

1. (a) R. Stewart in "Oxidation in Organic Chemistry, Part A," K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965, pp. 1-68
(b) F. Freeman, *Rev. React. Species Chem. React.*, 1, 179-226 (1976).
2. (a) K. B. Sharpless, R. F. Lauer, O. Repic, A. Y. Teranishi, and D. R. Williams, *J. Am. Chem. Soc.*, 93, 3303-3304 (1971); (b) K. B. Sharpless and D. R. Williams, *Tetrahedron Lett.*, 3045-3046 (1975).
3. (a) K. B. Wiberg and K. A. Saegebarth, *J. Am. Chem. Soc.*, 79, 2822-2824 (1957); (b) K. B. Wiberg and R. D. Greer, *ibid.*, 88, 5827-5832 (1966).
4. M. Jáky and L. I. Simándi, *J. Chem. Soc., Perkin Trans. 2*, 1481-1486 (1972).

5. L. I. Simándi and M. Jáky, J. Am. Chem. Soc., 98, 1995-1997 (1976).
6. (a) D. G. Lee and J. R. Brownridge, J. Am. Chem. Soc., 95, 3033-3034 (1973); (b) D. G. Lee and J. R. Brownridge, Can. J. Chem., 51, 2102-2104 (1973).
7. D. G. Lee and J. R. Brownridge, J. Am. Chem. Soc., 96, 5517-5523 (1974).
8. M. B. Allen and S. Ruben, J. Am. Chem. Soc., 64, 948-950 (1942).
9. Alkenes: (a) L. I. Simándi and M. Jáky, Inorg. Nucl. Chem. Lett., 7, 605-609 (1971); (b) N. T. Son, M. Jáky, and L. I. Simándi, ibid., 12, 291-296 (1976); (c) M. Jáky, L. I. Simándi, L. Maros, and I. Molnár-Perl, J. Chem. Soc., Perkin Trans. 2, 1565-1569 (1973); (d) L. I. Simándi and M. Jáky, ibid., 1856-1860 (1973); (e) L. I. Simándi and M. Jáky, ibid., 939-943 (1976); (f) Z. Szeverenyi, L. I. Simándi, and M. Jáky, Inorg. Chim. Acta, 23, L31-L32 (1977); (g) M. Jáky and L. I. Simándi, React. Kin. C., 3, 397-404 (1975); (h) K. Polgar, M. Jáky, and L. I. Simándi, ibid., 5, 489-495 (1976).
10. Alkynes: (a) L. I. Simándi and M. Jáky, J. Chem. Soc., Perkin Trans. 2, 2326-2330 (1972); (b) L. I. Simándi and M. Jáky, ibid., 1861-1866 (1973); (c) L. I. Simándi and M. Jáky, ibid., 630-633 (1977); (d) L. I. Simándi and M. Jáky, Tetrahedron Lett., 3489-3492 (1970).
11. L. I. Simándi, Magyar Kém. Folyóirat, 75, 269-273 (1969).
12. J. S. Littler, Tetrahedron, 27, 81-91 (1971).
13. (a) S. Iida and H. Hayatsu, Biochim. Biophys. Acta, 213, 1-13 (1970); (b) F. Freeman and E. M. Karchefski, ibid., 447, 238-245 (1976); (c) F. Freeman, C. O. Fuselier, and E. M. Karchefski, Tetrahedron Lett., 2133-2136 (1975).
14. D. J. Sam and H. E. Simmons, J. Am. Chem. Soc., 94, 4024-4025 (1972).
15. A. W. Herriott and D. Picker, Tetrahedron Lett., 1511-1514 (1974).

MECHANISMS OF CHEMIEXCITATION: 1,2-DIOXETANE SCHIZOPHRENIA REDUCED

Reported by Keith Horn

October 6, 1977

The intriguing phenomenon of bioluminescence¹ or chemiluminescence² has been the subject of numerous chemical investigations because of the fundamental process involved, *i.e.*, the thermal conversion of a ground state species to an excited state product capable of emitting a photon of light. The study of the unimolecular thermal decomposition of 1,2-dioxetanes,³ subsequent to their isolation in 1969⁴, has provided considerable insight into the mechanisms of chemiexcitation.

The mechanistic behavior of a 1,2-dioxetane along the reaction coordinate leading to excited state ketone products has been considered in terms of two general mechanisms.⁵ The first is the concerted ring opening in which both the carbon-carbon and oxygen-oxygen bonds are stretched simultaneously. This is a thermally forbidden [2+2] retro-cycloaddition in which a ground state correlates with an excited state product.⁶ The high yield of triplet ketone products can be explained in terms of vibronic or spin-orbit coupling.⁷ The second general mechanism for thermal decomposition of 1,2-dioxetanes postulates initial cleavage of the oxygen-oxygen bond to form a 1,4 biradical intermediate. Thermochemical calculations with comparison to cyclobutane decomposition support the biradical scheme, suggesting an activation barrier to reclosure to the dioxetane of approximately 11 kcal/mol.⁸

Recent *ab initio* studies (GVB-CI)⁹ concur with the biradical mechanism, placing the open OCCO biradical 14 kcal/mol above the ground state dioxetane and suggesting that the ground state dioxetane crosses three triplet states in opening to the biradical intermediate. CNDO CI¹⁰ calculations also favor a biradical intermediate, though MINDO/3¹¹ places the biradical higher in energy than the transition state for the concerted process. Experimental evidence presently favors the biradical mechanism. Initial evidence was found in the similarity of activation parameters for 3,3-dimethyl-1,2-dioxetane and 3-methyl-3-phenyl-1,2-dioxetane¹² as well as 3,3-diphenyl-1,2-dioxetane and 3,3-dibenzyl-1,2-dioxetane.¹³ The thermal stabilities of adamantylideneadamantane-1,2-dioxetane ($\Delta E_{act} = 35 \pm 2.0$ kcal/mol)¹⁴ and of 7,7'-binorbornylidene-1,2-dioxetane¹⁵ provide further support for this mechanism. The recent study of the isotopically labelled *trans*-3,4-diphenyl-3-deutero-1,2-dioxetane¹⁶ showed no secondary deuterium isotope effect on the rate of thermal decomposition. This was interpreted as being consistent only with a stepwise, biradical decomposition pathway. Further, no partitioning of excited state energy between protio- and deuteriobenzaldehydes was observed.

The thermolysis of unsymmetrical 1,2-dioxetanes can potentially result in either of two excited state ketone products. In 3,3-dibenzyl-1,2-dioxetane¹⁷ and 3-methyl-3-(2'-naphthyl)-7,7-diphenyl-1,2-dioxaspiro-[3.5]nona-5,8-diene¹⁸ where the excited state products are easily distinguishable, only one is detected in the excited state. These results have been explained in terms of energetics and a kinetic preference for $n-\pi^*$ triplets.^{10a,19} It has been shown that 3-acetyl-4,4-dimethyl-1,2-dioxetane produces both excited state acetone (triplet) and excited state methylglyoxal (singlet and triplet) in relatively high yield. The high yield of excited state α -dicarbonyl product may be interpreted in terms of the exothermic pathways available from a biradical intermediate to the excited states.

The photofragmentation of 1,2-dioxetanes to give low ratios of triplet to singlet excited carbonyl products is an example of an efficient adiabatic photoreaction.²⁰ The mechanism of the photoreaction of tetramethyl-1,2-dioxetane has been probed using picosecond spectroscopy.²¹ No biradical intermediate (of lifetime longer than 10 ps) on the reaction coordinate to excited singlet acetone was observed. Two IR laser photolysis studies of tetramethyl-1,2-dioxetane have also been reported.²²

A third general mechanism for chemiluminescence from 1,2-dioxetanes is potentially suggested by the recent report of the observation of chemically initiated electron exchange luminescence (CIEEL) from diphenoyl peroxide.²³ This process involves a radical anion, radical cation annihilation, similar to that in electrogenerated chemiluminescence.²⁴ The observation that the singlet yield from 3,4-dianthryl-1,2-dioxetanes is increased in the presence of silica gel,²⁵ suggests that under appropriate conditions, the thermal decomposition of 1,2-dioxetanes may proceed by an intramolecular CIEEL type mechanism.

BIBLIOGRAPHY

1. (a) W. Adam, *J. Chem. Ed.*, 52, 138 (1975); (b) E. H. White, J. D. Miano, and M. Umbreit, *J. Am. Chem. Soc.*, 97, 198 (1975); (c) E. H. White and B. R. Branchini, *J. Am. Chem. Soc.*, 97, 1243 (1975); (d) F. McCapra, *Acc. Chem. Res.*, 9, 201 (1976).
2. (a) F. McCapra, "Progress in Organic Chemistry," 8, 231 (1973); (b) E. H. White, J. D. Miano, C. J. Watkins, and E. J. Breau, *Angew. Chem., Int. Ed. Eng.*, 13, 229 (1974).
3. T. Wilson, *Int. Rev. Sci., Phys. Chem., Ser. Two*, 9, 265 (1976).
4. K. R. Kopecky and C. Mumford, *Can. J. Chem.*, 47, 709 (1969).
5. N. J. Turro, P. Lechtken, N. E. Schore, G. Schuster, H.-C. Steinmetzer, and A. Yekta, *Acc. Chem. Res.*, 7, 97 (1974).
6. (a) F. McCapra, *Chem. Commun.*, 155 (1968); (b) D. R. Kearns, *J. Am. Chem. Soc.*, 91, 6654 (1969).
7. (a) N. J. Turro and P. Lechtken, *J. Am. Chem. Soc.*, 95, 264 (1973); (b) N. J. Turro and A. Devaquet, *J. Am. Chem. Soc.*, 97, 3859 (1975).
8. H. E. O'Neal and W. H. Richardson, *J. Am. Chem. Soc.*, 92, 6553 (1970).
9. L. B. Harding and W. A. Goddard III, *J. Am. Chem. Soc.*, 99, 4520 (1977).
10. (a) E. M. Evleth and G. Feler, *Chem. Phys. Letters*, 22, 499 (1973); (b) K. Yamaguchi and T. Fueno, *Chem. Phys. Letters*, 22, 466 (1973).
11. M. J. S. Dewar and S. Kirschner, *J. Am. Chem. Soc.*, 96, 7578 (1974).
12. (a) W. H. Richardson, M. B. Yelvington, and H. E. O'Neal, *J. Am. Chem. Soc.*, 94, 1619 (1972); (b) W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and G. Ranney, *J. Am. Chem. Soc.*, 96, 4045 (1974).
13. W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and H. E. O'Neal, *J. Am. Chem. Soc.*, 96, 7525 (1974).
14. G. B. Schuster, N. J. Turro, H.-C. Steinmetzer, A. P. Schaap, G. Feler, W. Adam, and M. S. Ho, *J. Am. Chem. Soc.*, 97, 7110 (1975).
15. P. D. Bartlett and M. S. Ho, *J. Am. Chem. Soc.*, 96, 627 (1974).
16. Ja-young Koo and G. B. Schuster, *J. Am. Chem. Soc.*, 99, 5403 (1977).
17. W. H. Richardson, F. C. Montgomery, and M. B. Yelvington, *J. Am. Chem. Soc.*, 94, 9277 (1972).
18. H. E. Zimmerman, G. E. Keck, and J. L. Pfladerer, *J. Am. Chem. Soc.*, 98, 5574 (1976).

19. (a) D. R. Kearns, Chem. Rev., 71, 345 (1971); (b) D. R. Roberts, J. Chem. Soc., Chem. Commun., 683 (1974); (c) N. J. Turro and A. Devaquet, J. Am. Chem. Soc., 97, 3859 (1975).
20. P. Lechtken and H.-C. Steinmetzer, Chem. Ber., 108, 3159 (1975).
21. K. K. Smith, Ja-young Koo, G. B. Schuster, and K. J. Kaufmann, Chem. Phys. Letters, 48, 267 (1977).
22. (a) W. E. Farneth, G. Flynn, R. Slater, and N. J. Turro, J. Am. Chem. Soc., 98, 7877 (1977); (b) Y. Haas and G. Yahav, Chem. Phys. Letters, 48, 63 (1977).
23. Ja-young Koo and G. B. Schuster, J. Am. Chem. Soc., 99, 6107 (1977).
24. L. R. Faulkner, Int. Rev. Sci., Phys. Chem., Ser. Two, 9, 213 (1976).
25. A. P. Schaap, presented at the 174th National Meeting of the American Chemical Society, Chicago, Illinois, August 1977.

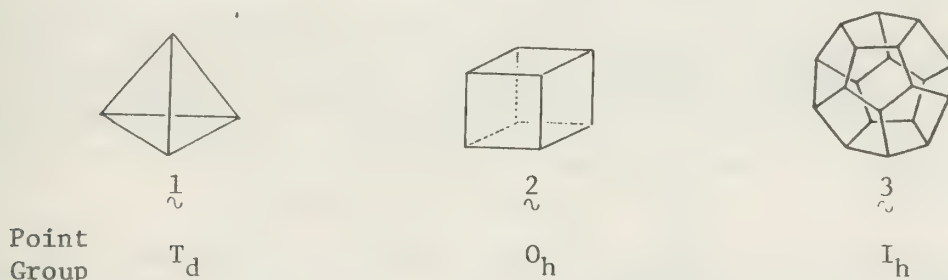
ORGANIC CHEMISTRY AND THE PLATONIC SOLIDS

Reported by Dennis Stack

October 10, 1977

Little did Plato realize that the five regular polyhedra mentioned in his *Theaetetus* would create such a topic of interest in modern chemistry.¹ The so-called Platonic solids or uniform polyhedra may be defined simply as geometric solids, each being composed of regular polygons and containing equivalent vertices and edges. These five solids are the tetrahedron, hexahedron (cube), octahedron, dodecahedron, and the icosahedron. Due to the tetravalent nature of carbon, only the tetrahedron, hexahedron (cube), and the dodecahedron can have hydrocarbon equivalents, *viz.* tetrahedrane (1), cubane (2), and dodecahedrane (3).²

Figure 1



Much of the interest in these compounds lies in their exceptionally high symmetry. The tetrahedral point group (T_d), for example, has 24 identity operations while the icosahedral point group (I_h) with its 120 operations is the most symmetrically possible geometric solid.³ In addition to the "pleasing aesthetic qualities" of these compounds, it was evident that much new chemical information would evolve during their syntheses. A more recent aspect to the interest in these compounds lies in the unusual thermodynamic properties which they may exhibit. At the present time, only cubane has been prepared while the syntheses of tetrahedrane and dodecahedrane, or derivatives thereof, are still being pursued.

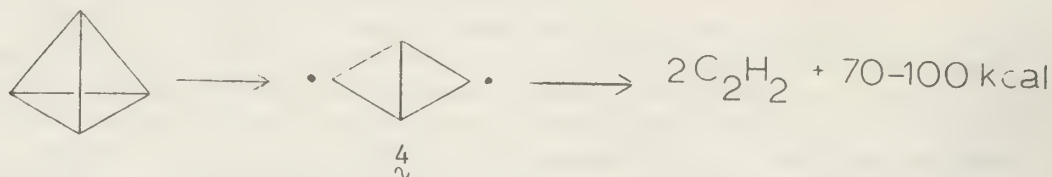
These compounds, especially tetrahedrane, have been the subject of many theoretical calculations and Table 1 summarizes, in part, the calculated thermodynamic parameters. From the values for the strain energies per carbon-carbon bond, it is apparent that dodecahedrane will be a relatively stable molecule. However, in the case of tetrahedrane, the

Table 1. Calculated Thermodynamic Parameters for the Platonic Solids

	Calcd(Obsvd) ΔH_f [kcal/mole]	Strain Energy [kcal/mole]	Strain Energy per Carbon [kcal/g-atom]	Ref.
Tetrahedrane	129-137	130-138	32-34	4
Cubane	149(149)	166	20.8	5
Dodecahedrane	-0.2-45.3	43.0-88.4	2.2-6.6	5

strain energy per carbon atom of 32-34 kcal/g-atom is greater than any known compound and calculations have predicted tetrahedrane to be 70 to 84 kcal/mole less stable than its unisolated valence isomer cyclobutadiene.^{6,7}

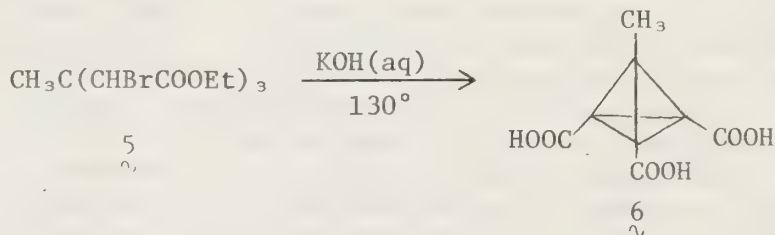
Decomposition of tetrahedrane to acetylene through a concerted process is thermally forbidden but may proceed by a two step process via the diradical 4.⁸ Calculations have estimated this process to be exothermic by 70 to



100 kcal/mole. Unfortunately, this diradical is approximately thermo-neutral⁷ with tetrahedrane or ca. 20 kcal/mole⁴ higher in energy, depending on the calculations chosen. Despite its instability, Baird and Dewar have predicted tetrahedrane to have a lifetime of 10 seconds at -40°C.⁷

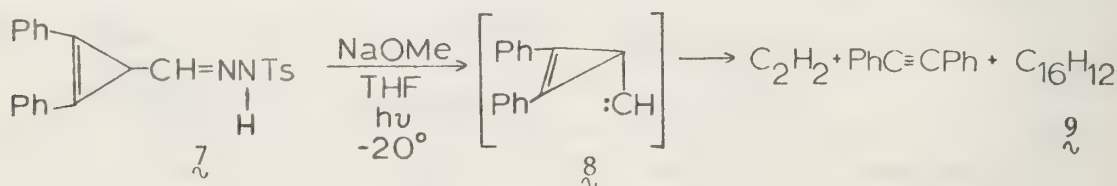
It is interesting to note that two stable tetrahedral molecules are known in the realm of inorganic chemistry. The first example, white phosphorus P₄ exists in the solid and liquid phases, as well as in the gas phase up to 800°C as a tetrahedral molecule.⁹ The other known tetrahedral molecule is a boron halide, (BCl)₄, which is a solid and stable up to 200°C.¹⁰

Tetrahedrane. Attempts at the syntheses of tetrahedrane derivatives date back to 1913 when Beesley and Thorpe¹¹ reported the synthesis of a stable, caged ring tricarboxylic acid which was formed upon the addition of the tribromoester 5 to concentrated aqueous potassium hydroxide at 130°.



In 1920, these same authors reported yet another synthesis of the alleged tetrahedrane derivative (6).¹² However, in 1959, Woodward and Larson¹³ were unable to reproduce the work of Beesley and Thorpe and instead isolated β:β-dimethylpropanetricarboxylic and acetic acids from the reaction.

In 1965, a more plausible synthetic plan was used by Masamune and Kato from which they reported the synthesis of 1,2-diphenyltetrahedrane.¹⁴ Treatment of the tosylhydrazone 7 with sodium methoxide under photolytic



conditions yielded a carbene (8). This carbene, upon rearrangement, afforded acetylene, diphenylacetylene, and an unknown compound (9) in 0.05 to 0.1% yield. This new compound gave the proper combustion analysis for C₁₆H₁₂ and the reported pmr spectrum appeared to be consistent for such a structure.

Table 2. Acetylene Yields

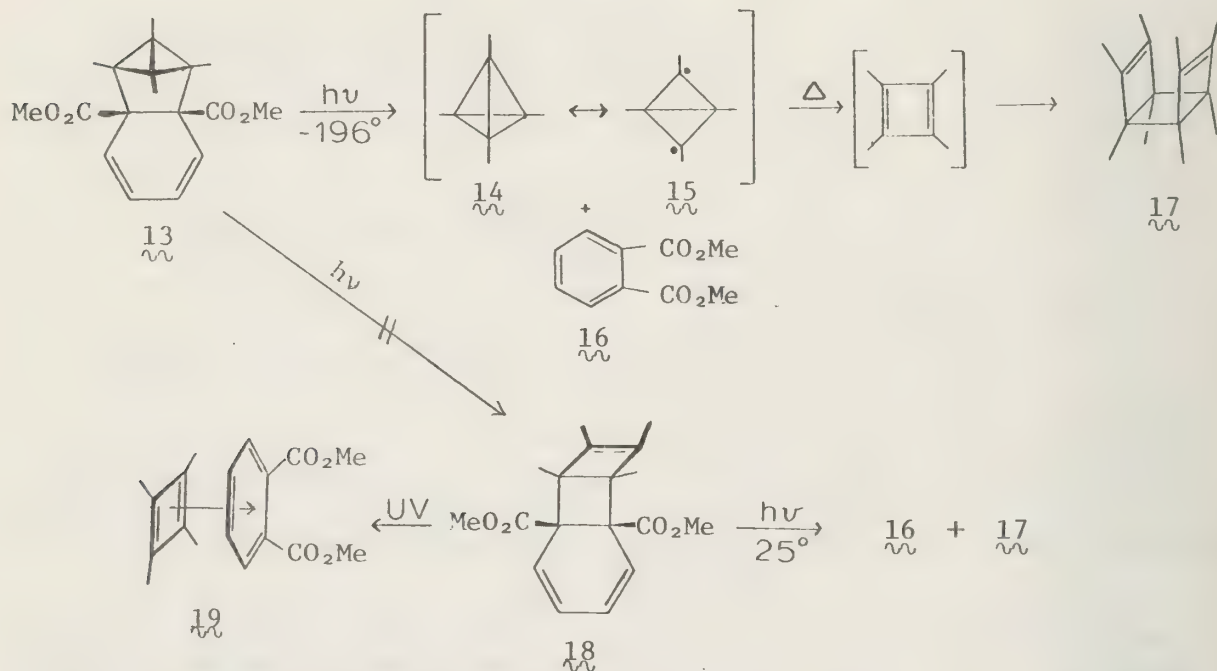
	Exp [%]	Calcd [%]
C ₂ H ₂	23.7	25.0
C ₂ HD	63.6	62.4
C ₂ D ₂	12.8	12.6

Table 3. Activity Distribution

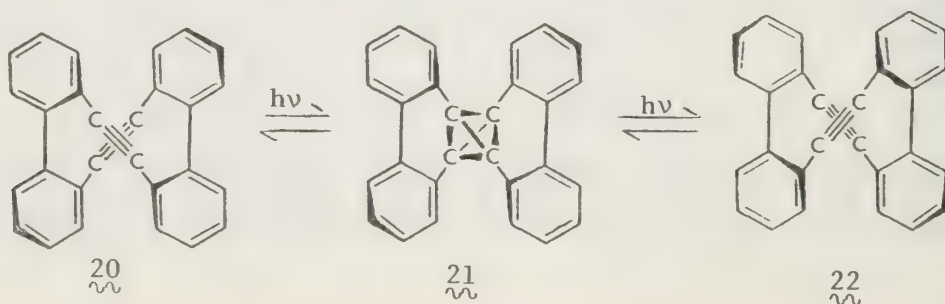
	Exp [%]	Calcd [%]
C ₂ H ₂	13.8	9.2
C ₂ HD	59.4	65.6
C ₂ D ₂	26.8	25.2

phthalate (16) and the dimer (17) of tetramethylcyclobutadiene (Scheme I). This observation can best be explained by the formation of tetramethyl-tetrahedrane (14) which decomposes to tetramethylcyclobutadiene (possibly via the diradical 15) upon warming. In an alternative mechanism which may be postulated, 13 is first converted into its isomer 18 which has been shown to decompose to dimethylphthalate (16) and the dimer 17. This mechanism can be discarded, however, since 18 cannot be isolated as an intermediate and since the expected charge transfer complex 19, which appears at 385 nm, could not be detected in the low temperature UV spectrum.

Scheme I



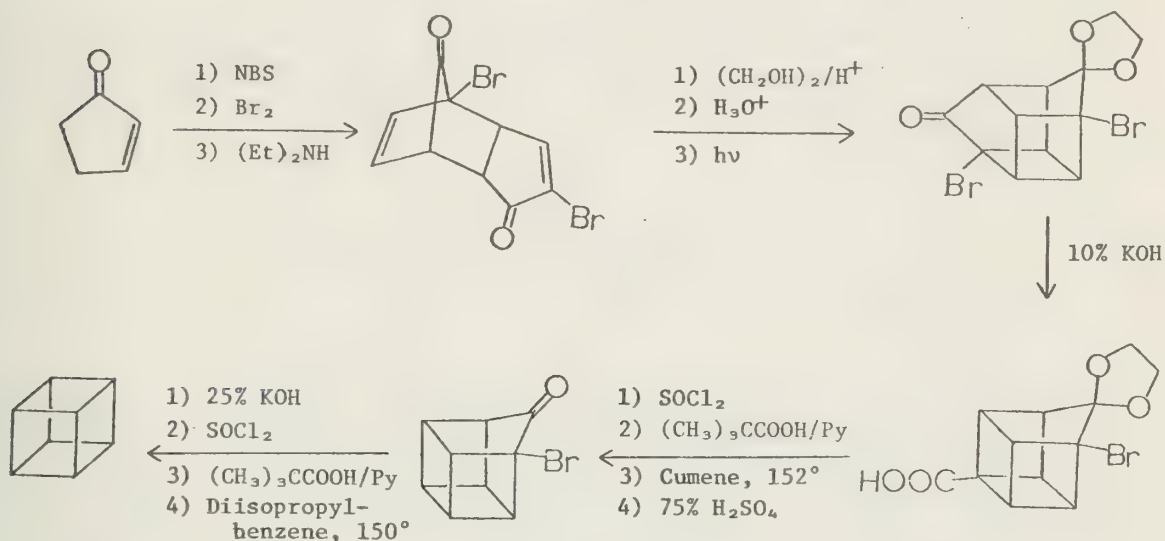
Another approach to tetrahedrane or a tetrahedrally symmetric intermediate has been postulated by Staab.^{29a-c} The triple bonds in compound 20 are oriented properly for a photochemical cycloaddition. Subsequent



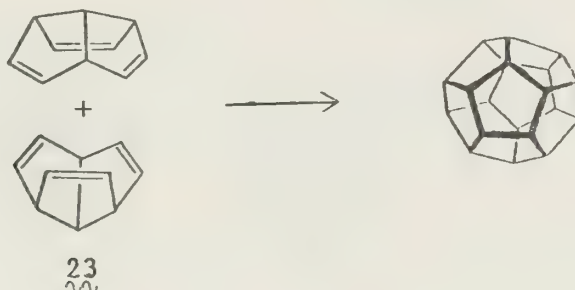
decomposition of the tetrahedrane intermediate (21) would yield either the starting material (20) or its mirror image (22).

Cubane. Attempts at the synthesis of cubane have fared much better, the first derivatives of C_8H_8 hydrocarbon having been prepared by Eaton and Cole³⁰ in 1964. Shortly thereafter, these same authors reported the synthesis of the parent hydrocarbon itself³¹ (Scheme II). Two other synthesis of cubane have also been reported.^{32,33}

Scheme II. Cubane synthesis by Eaton and Cole

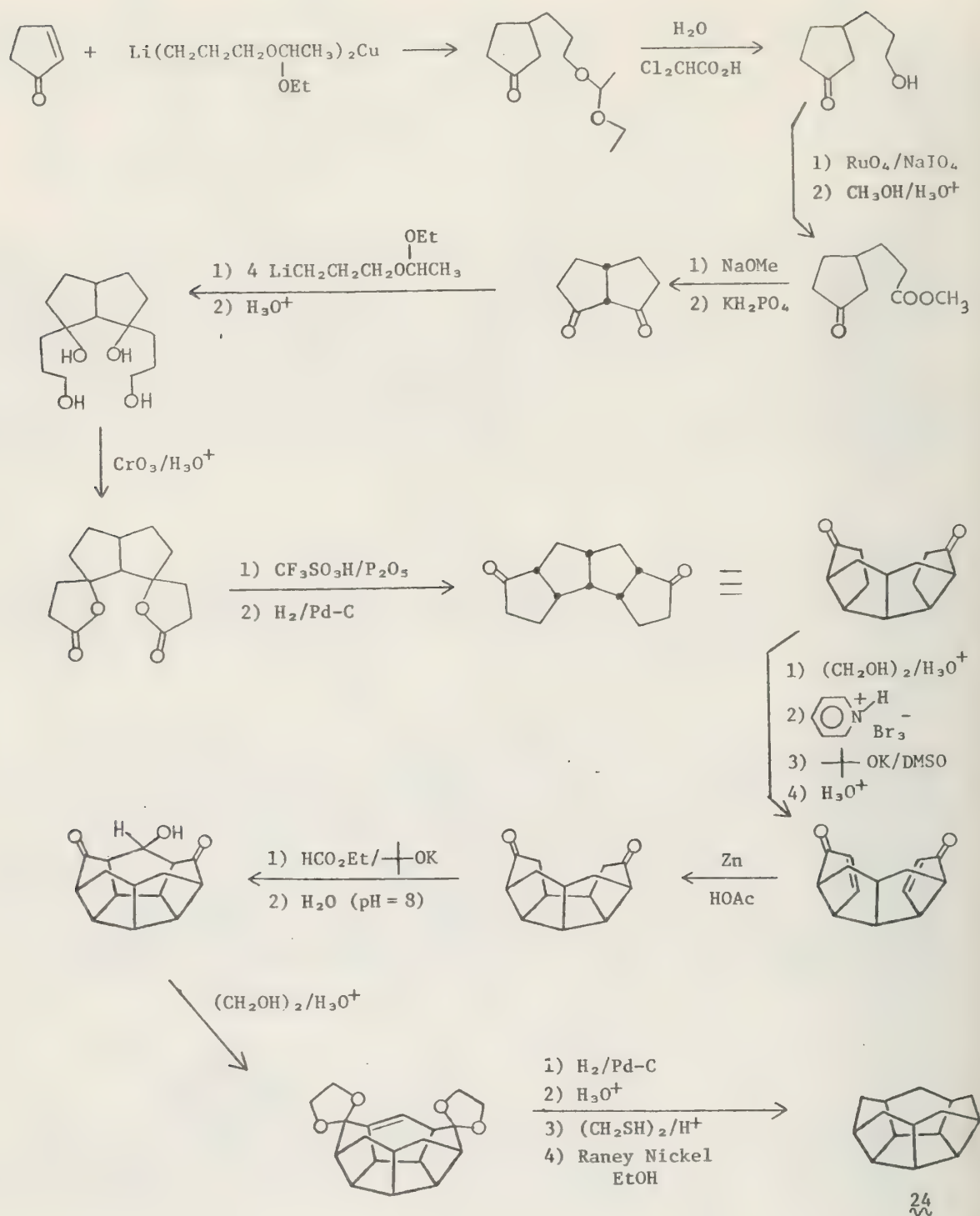


Dodecahedrane. The last member of the family, dodecahedrane, presents a formidable synthetic challenge. Woodward's approach,³⁴ which was the first reported attempt at its synthesis, involved as the key step, the dimerization of triquinacene (23). Although the synthesis of triquinacene itself was successful, no evidence was found for its subsequent dimerization. In another reported synthesis of triquinacene,³⁵ it was suggested that a transition metal might effect the dimerization and it was even speculated that the metal atom might be trapped within the dodecahedrane cage.

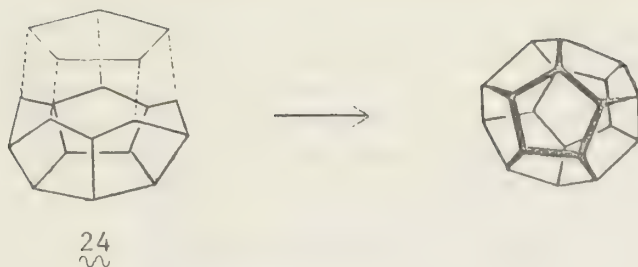


Eaton's approach to dodecahedrane involves "capping" the peristylane system (24) with a cyclopentane unit. In 1972, he published the first synthesis of a substituted peristylane system³⁶ and later, the hydrocarbon itself (Scheme III).³⁷ Fusing the "cap" to one of the carbons of a peri-

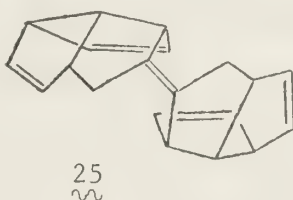
Scheme III. Eaton's synthesis of peristylane



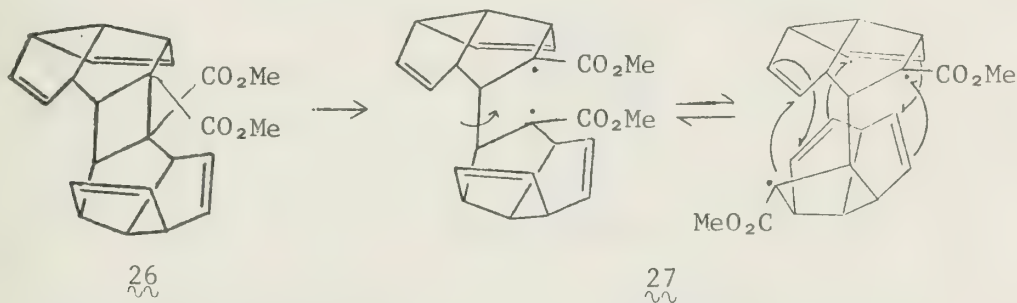
stylane model system has been successful,³⁸ but closure of the remaining bonds has yet to be achieved.



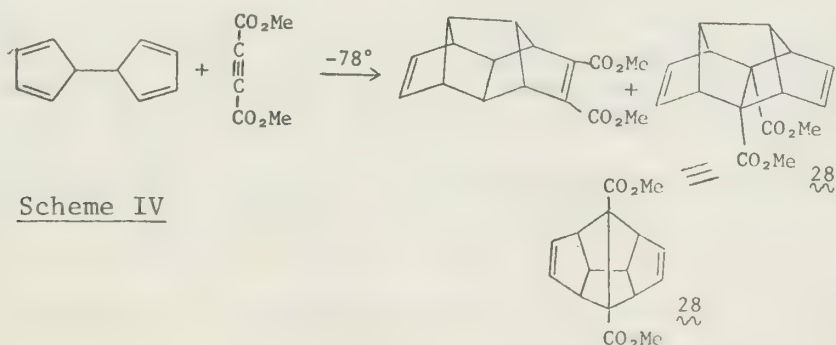
The use of two endo,endo coupled triquinacene units to bring the two subunits closer to the proper orientation for subsequent coupling presents another interesting approach. Utilization of compounds with structures such as 25 in the elaboration of the dodecahedrane molecule is presently being pursued by Paquette.^{39a-c}



In another synthetic approach by Woodward and Repić,⁴⁰ it was postulated that the dimer of (+)-methyltriquinacene-2-carboxylate (26) could be used to generate the diradical 27, which could close to the dodecahedrane structure. The carbomethoxy groups present serve to stabilize the diradical, thus extending its lifetime sufficiently for rotation to occur and to prevent cleavage of both cyclobutane bonds yielding two molecules of triquinacene. However, inability to obtain compound 26 has not allowed this idea to be tested in practice.

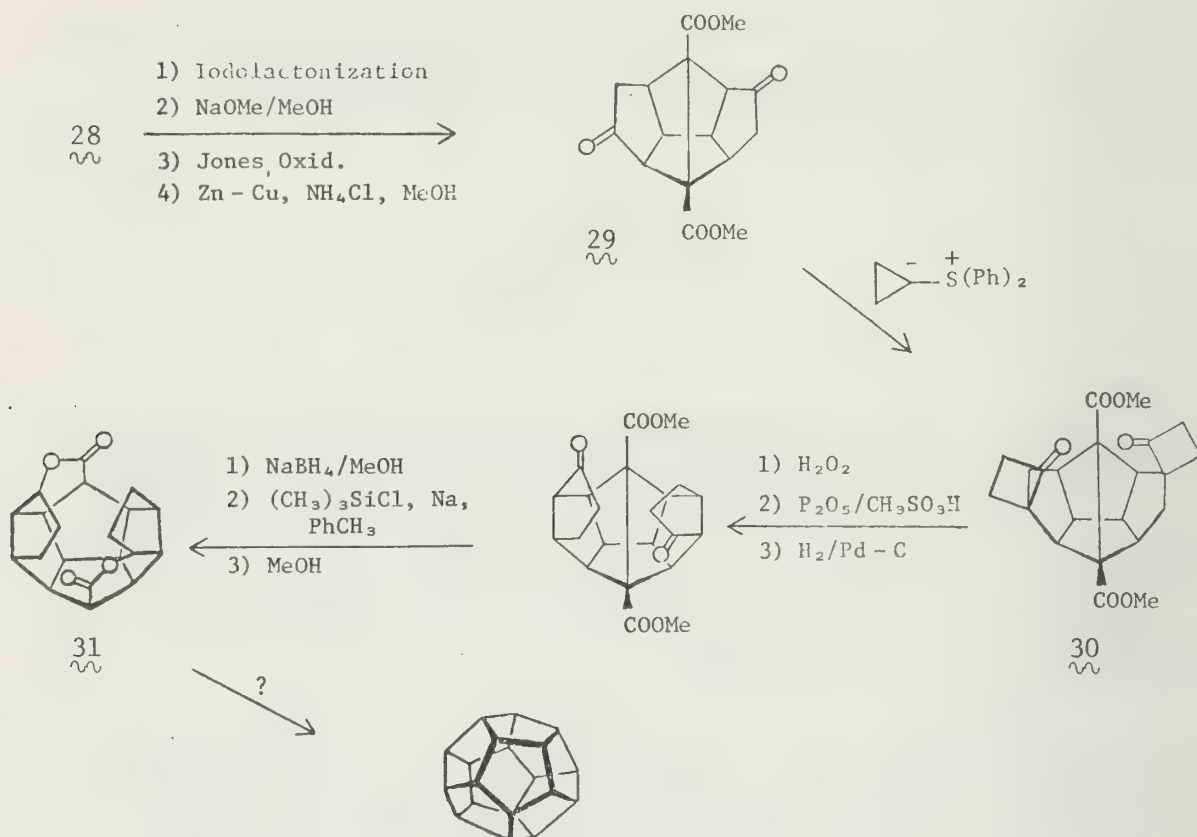


Paquette's second approach to dodecahedrane makes use of the "Domino" Diels-Alder reaction^{41a,b} (Scheme IV) which yields the diester 28 as a starting material.⁴²



Elaboration of this molecule (Scheme V) has thus far resulted in the formation of compound 31, the structure of which has been determined by x-ray structure analysis. It is interesting to note that compound 29 contains all the carbons necessary, and only the carbons necessary, for the dodecahedrane target molecule. At present, the closure of the remaining bonds in compound 31 to yield the dodecahedrane framework is actively being pursued by Paquette and coworkers.

Scheme V. Synthetic approach by Paquette



BIBLIOGRAPHY

1. H. S. M. Coxeter, "Encyclopaedia Britannica", Encyclopedia Britannica, Inc., Chicago, Illinois, 1970, Vol. 20, p. 860.
2. The systematic names for these compounds are: tetrahedrane, tricyclo-[1.1.0.0^{2,4}]butane; cubane, pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane; and dodecahedrane, undecacyclo[9.9.0.0^{2,9}.0^{3,7}.0^{4,20}.0^{5,18}.0^{6,16}.0^{8,15}.0^{10,14}.0^{12,19}.0^{13,17}]eicosane.
3. F. A. Cotton, "Chemical Applications of Group Theory", 2nd ed., Wiley-Interscience, New York, N.Y., 1971, pp. 39-45.
4. J. M. Schulman and T. J. Venanzi, J. Am. Chem. Soc., 96, 4739 (1974).
5. E. M. Engler, J. D. Andose, and P. v. R. Schleyer, J. Am. Chem. Soc., 95, 8005 (1973).
6. R. J. Buenker and S. D. Peyerimhoff, J. Am. Chem. Soc., 91, 4342 (1969).
7. N. C. Baird and M. J. S. Dewar, J. Am. Chem. Soc., 89, 3966 (1967).
8. R. F. Peterson, Jr., R. T. K. Baker, and R. L. Wolfgang, Tetrahedron Lett., 4749 (1969).
9. F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3rd ed., Interscience, New York, N.Y., 1972, p. 370

10. F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3rd ed., Interscience, New York, N.Y., 1972, p. 236.
11. R. M. Beesley and J. F. Thorpe, Proc. Chem. Soc., 29, 346 (1913).
12. R. M. Beesley and J. F. Thorpe, J. Chem. Soc., 117, 591 (1920).
13. H. O. Larson and R. B. Woodward, Chem. Ind. (London), 193 (1959).
14. S. Masamune and M. Kato, J. Am. Chem. Soc., 87, 4190 (1965).
15. S. Masamune and M. Kato, J. Am. Chem. Soc., 88, 610 (1966).
16. E. H. White, G. E. Maier, R. Craeve, U. Zirngibl, and E. W. Friend, J. Am. Chem. Soc., 88, 611 (1966).
17. S. H. Bauer and P. Jeffers, J. Am. Chem. Soc., 87, 3278 (1966).
18. S. A. Kandil and R. E. Dessy, J. Am. Chem. Soc., 88, 3027 (1966).
19. G. L. Closs and V. N. M. Rao, J. Am. Chem. Soc., 88, 4116 (1966).
20. N. Obata and I. Moritani, Bull. Chem. Soc. Jap., 39, 2250 (1966).
21. H. W. Chang, A. Lautzenheimer, and A. P. Wolf, Tetrahedron Lett., 6295 (1966).
22. E. H. White and A. F. Siebers, Tetrahedron Lett., 2713 (1967).
23. H.-K. Lee, Daehan Hwahak Hwoejee, 13, 347 (1969); Chem. Abstr., 73, 87340q (1969).
24. H. Ona, H. Yamaguchi, and S. Masamune, J. Am. Chem. Soc., 92, 7495 (1970).
25. P. B. Shevlin and A. P. Wolf, J. Am. Chem. Soc., 92, 406, 5291 (1970).
26. R. T. Mullen and A. P. Wolf, J. Am. Chem. Soc., 84, 3214 (1962).
27. M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds", Academic Press, New York, N.Y., 1967, p. 69.
28. G. Maier, Angew. Chem., Int. Ed. Engl., 13, 425 (1974).
29. (a) H. A. Staab and E. Wehinger, Angew. Chem. Int. Ed. Engl., 7, 225 (1968); (b) H. A. Staab, H. Mack, and E. Wehinger, Tetrahedron Lett., 1465 (1968); (c) H. A. Staab, E. Wehinger, and W. T. Thorwart, Chem. Ber., 105, 2290 (1972).
30. P. E. Eaton and T. W. Cole, J. Am. Chem. Soc., 86, 962 (1964).
31. P. E. Eaton and T. W. Cole, J. Am. Chem. Soc., 86, 3157 (1964).
32. C. G. Chin, H. W. Cuts, and S. Masamune, Chem. Commun., 880 (1966).
33. J. C. Borborak, L. Watts, and W. R. Pettit, J. Am. Chem. Soc., 88, 1328 (1966).
34. R. B. Woodward, T. Fukunaga, and R. C. Kelly, J. Am. Chem. Soc., 86, 3162 (1964).
35. T. Jacobson, Acta Chem. Scand., 21, 2235 (1967).
36. P. E. Eaton and R. H. Mueller, J. Am. Chem. Soc., 94, 1014 (1972).
37. P. E. Eaton, R. H. Mueller, G. R. Carlson, D. A. Cullison, G. F. Cooper, T.-C. Chou, and E. P. Krebs, J. Am. Chem. Soc., 99, 2751 (1977).
38. P. E. Eaton, presented in part at the Xth Great Lakes Regional Meeting of the American Chemical Society, Evanston, Illinois, June, 1976.
39. (a) L. A. Paquette, S. V. Ley, and W. B. Farnham, J. Am. Chem. Soc., 96, 312 (1974); (b) L. A. Paquette, W. B. Farnham, and S. V. Ley, ibid., 97, 7273, 7280 (1975); (c) L. A. Paquette, I. Itoh, and K. B. Lipkowitz, J. Org. Chem., 41, 3524 (1976).
40. O. Repić, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1976.
41. (a) L. A. Paquette and M. J. Wyvratt, J. Am. Chem. Soc., 96, 4671 (1974); (b) D. MacNeil, B. R. Vogt, J. J. Sudol, S. Teodoropulos, and E. Hedaya, ibid., 96, 4673 (1974).
42. L. A. Paquette, M. J. Wyvratt, O. Schallner, D. F. Schneider, W. J. Begley, and R. M. Blankenship, J. Am. Chem. Soc., 98, 6744 (1976).

SYNTHESIS OF OPTICALLY ACTIVE α -AMINO ACIDS

Reported by Michael R. Kilbourn

October 13, 1977

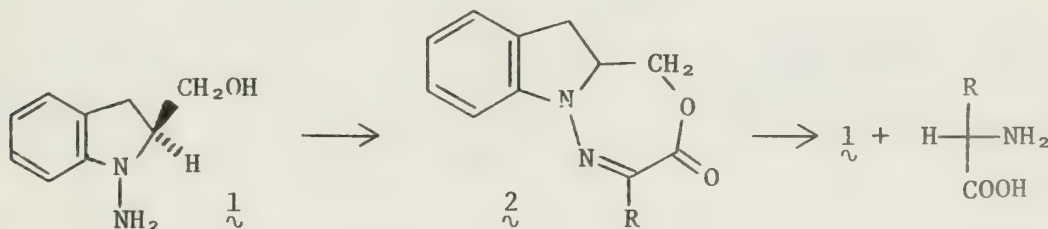
The preparation of α -amino acids has been accomplished by three principal methods: (1) separation from protein hydrolysates, (2) fermentation, and (3) chemical synthesis. As almost all commercially produced amino acids are ultimately intended for human or animal consumption, the preparation of only the L-isomers is usually desired. This is inherent in protein hydrolysis or bacterial fermentation (bacteria generally produce the L-isomer with the exception of alanine, where racemic mixtures are usually produced), but recovery of optically pure amino acids from chemical synthesis has required resolution of racemic mixtures (by fractional crystallization).¹

Recently, much attention has been focused on the asymmetric synthesis of α -amino acids. Chemical methods which would yield only one optical isomer (and, preferably, the L-isomer) would obviate the need for a resolution step, and might improve both the speed of the synthesis and the overall yield of optically pure product. Such synthetic approaches would not only be of commercial value, but would also serve as the organic chemist's answer to the enzyme-pyridoxal phosphate transamination reaction as found in nature.²

This review shall include only those advances in asymmetric synthesis of α -amino acids since 1970, which have been partially reviewed by Thomson,³ Bell and John,⁴ and Weinges and Stemmle.⁵ Older methods of synthesis of optically active amino acids have been discussed by Dammann.⁶ General discussion of asymmetric organic reactions can be found in the works of Morrison and Mosher⁷ and Scott and Valentine.⁸

To avoid confusion over stereochemistry of intermediates and final amino acid products, the designation of amino acids as D- or L-isomers will not be used, and the configuration of all chiral molecules will be designated using the R,S notation of Cahn, Ingold, and Prelog.⁹

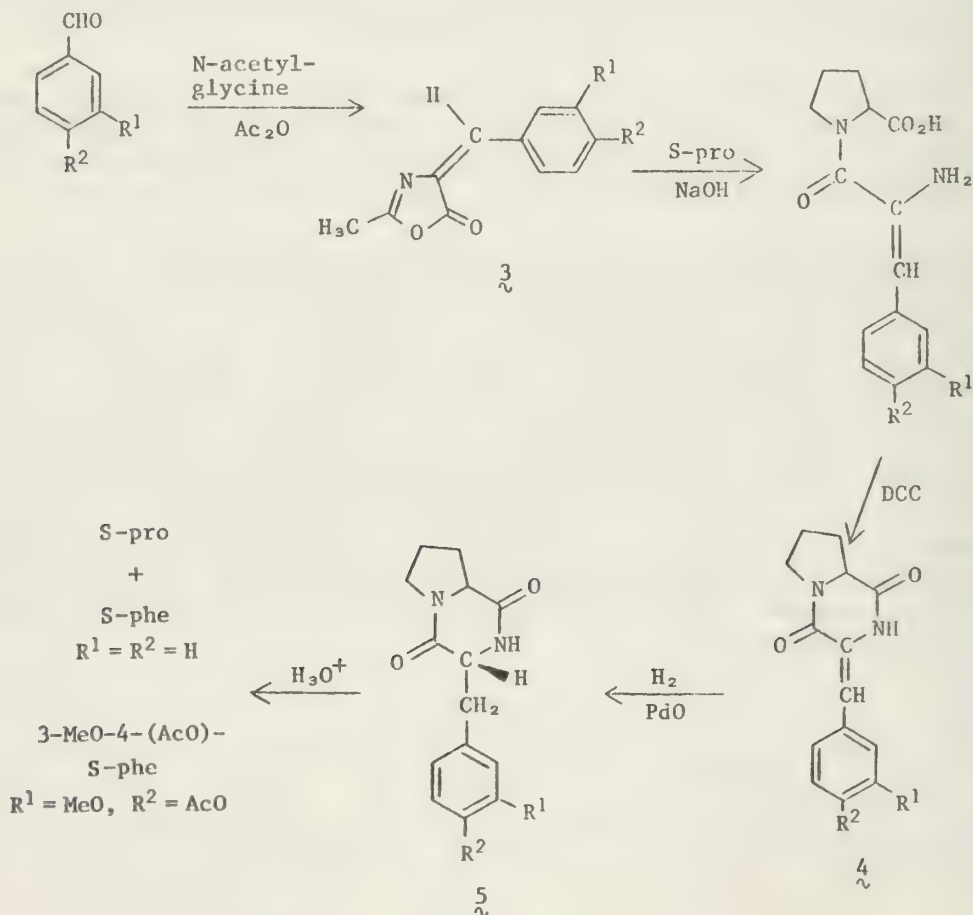
Synthesis Via Heterogeneous Catalytic Hydrogenation. The first synthesis of α -amino acids by asymmetric reduction using a heterogeneous catalyst, in which both high optical purities and recovery of the chiral reagent were realized, was described by Corey and coworkers in 1970.^{10,11} The reaction of α -ketoacid methyl esters with optically active (S)-N-amino-2-hydroxymethylindolines (**1**) yielded, in two steps, the hydrazono lactone **2**, which was reduced with aluminum amalgam and the ring opened to yield the optically active amino acid and (S)-2-hydroxymethylindoline, the latter converted by nitrosation and reduction to regenerated chiral reagent **1**. By that method, R-alanine and R-butyryne were prepared in 80 and 90% optical purities, respectively. This synthesis suffers, however, from the need of synthesizing the chiral reagent **1**, which was prepared in only 30% yield (5 steps) from ethyl 2-indolecarboxylate.

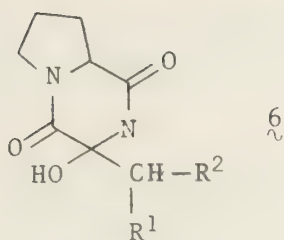


A simpler synthesis of aryl amino acids by heterogeneous catalytic reduction has been reported by Poisel and Schmidt.¹² Condensation of aromatic aldehydes with acetylglycine yielded the benzylidene-oxazolinone **3**, which upon treatment with S-proline and base gave the dipeptide. Use of dicyclohexylcarbodiimide (DCC) promoted cyclization to the arylidenedioxopiperazine **4**. Catalytic hydrogenation then afforded the saturated dioxopiperazine **5**, with optical purities greater than 90%; acid hydrolysis yielded the optically active α -amino acid and S-proline. The authors prepared S-phenylalanine and S-DOPA (3,4-dihydroxyphenylalanine, a precursor to dopamine and norepinephrine), but were unable to extend the synthesis to alkyl amino acids.

That extension, slightly modified, was accomplished by Bycroft and Lee.¹³ Using DCC, S-proline methyl ester was coupled with an α -keto acid to give the N- α -ketoacyl derivative, which upon standing in dry dimethoxyethane containing anhydrous ammonia cyclized to the hydroxydioxopiperazine **6**. Dehydration to an alkylidene-dioxopiperazine with trifluoroacetic acid or SOCl_2 /pyridine, followed by hydrogenation with Adam's catalyst, gave the saturated dioxopiperazine again in optical purities greater than 90%. In this manner, S-alanine was prepared in 60% overall yield. Hydrogenation of alkylidene-dioxopiperazines formed with S-phenylalanine or S-alanine gave considerably lower optical purities.

These synthetic approaches using S-proline as the chiral reagent are an improvement over the Corey synthesis, as optically pure proline is readily available from natural sources.





$R^1 = R^2 = H$, alanine

$R^1 = H$, $R^2 = CH(CH_3)_2$, leucine

$R^1 = CH_3$, $R^2 = CH_2CH_3$, isoleucine

Synthesis Via Homogeneous Catalytic Hydrogenation. Efficient asymmetric reduction of non-chiral α -acylaminoacrylic acids was first reported by Dang and Kagan in 1971.^{14,15} Using a chiral bisphosphine ligand, 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (diop,⁷), they prepared a chiral, soluble rhodium complex $[Rh(diop)(Cl)(S)]$ ($S = \text{solvent}$). With that catalyst, α -acetamidocinnamic acid was reduced quantitatively to (R)-N-acetylphenylalanine in 72% optical purity. Optical purities of other amino acids prepared with that catalyst are shown in Table 1.

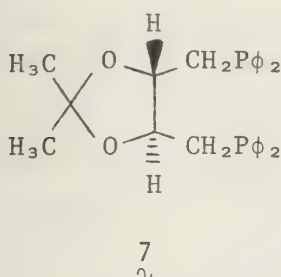
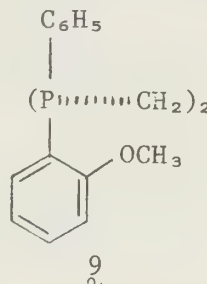
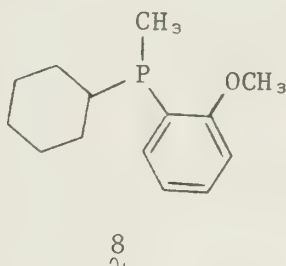


Table 1. Reduction With Rhodium-diop Catalyst ⁷

Product	Optical Purity	%	Yield
N-acetyl-(R)-ala	73		96
N-acetyl-(R)-tyr	80		92
N-acetyl-(R)-leu	22		98

Shortly after the report by Dang and Kagan, Knowles *et al.* described the preparation of chiral rhodium complexes, where the chirality lay on the phosphorus atom instead of the side chain.¹⁶ Various combinations of methyl, cyclohexyl, phenyl, and o-anisyl substituents were investigated, with the best results achieved with an o-anisylmethylcyclohexylphosphine ligand (8). Optical purities obtained were slightly better than those of Kagan (Table 2). Knowles has since then improved the optical purities achieved, by using the bisphosphine 1,2-bis-(o-anisylphenylphosphino)ethane ⁹; 3-methoxy-4-acetoxypheylalanine was prepared in 94% optical purity, and S-phenylalanine in 95%.^{17,18}



In an example that closely resembles the earlier use of proline as a chiral directing reagent for heterogeneous reduction, Achiwa¹⁹ has recently reported the preparation of a chiral bisphosphine, (2S,4S)-N-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM, ¹⁰), prepared in five steps from S-hydroxyproline. Optical purities of amino acids obtained using this ligand (Table 3) are greater than 85%.

Chiral complexes of ruthenium with Kagan's diop ligand have also been utilized in asymmetric reduction.²⁰ At present, a complex of rhodium is

being used commercially in the synthesis of S-DOPA.²¹ The use of rhodium with a functionalized cellulose support has been investigated, but chemical yields were low.²²

Table 2. Reduction of α -Acylaminoacrylic Acids With Rhodium-(o-anisylmethylcyclohexylphosphine) Complex

Product	Optical Purity, %
(S)-3-MeO-4 (AcO)-N-acetyl-DOPA	88
(S)-N-acetyl-phe	85
(S)-N-acetyl-ala	60

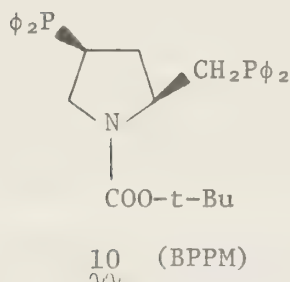


Table 3. Reduction of α -Acylaminoacrylic Acids With Rhodium-BBPM Catalyst

Product	Optical Purity, %
(S)-3-MeO-4 (AcO)-N-acetyl-DOPA	91
N-acetyl-(S)-phe	87
N-acetyl-4 (AcO)-(S)-tyr	86

Homogeneous catalytic hydrogenation holds promise as a powerful method for the synthesis of numerous optically active amino acids. α,β -Unsaturated- α -amino acids can be prepared by a variety of routes,²³ and smoothly hydrogenated using small quantities (0.01 molar equivalents) of soluble, chiral rhodium catalysts. Kagan and coworkers have examined the mechanism of the reduction, and attribute the high optical purities obtained to a rapid cis-addition of hydrogen to the double bond, held in position by formation of a π -complex with the rhodium.²⁴

Synthesis Via Addition to Schiff Bases. Hydrogen cyanide (HCN) undergoes rapid addition to the C=N bond of imines, Schiff bases, hydrazones, oximes, and similar compounds. This reaction has been used in the synthesis of optically active amino acids, by incorporating chirality into the molecule undergoing addition.

Originally, Patel and Worsley²⁵ reported the synthesis of amino acids in high (98-99%) optical purities by the addition of HCN to the Schiff base formed from (+) or (-) α -phenethylamine and an aliphatic aldehyde. Furthermore, the configuration of the amino acid was dependent on the configuration of the amine used; R-(+)- α -phenethylamine gave R-(-)-amino acid, and the S-(-)-isomer gave the S-(+)-amino acid. Later workers, however, questioned the results of Patel and Worsley. Harada and Okawara²⁶ reinvestigated the same reaction, but in their work analyzed the products as the 2,4-dinitrophenyl (DNP) derivatives; this was to eliminate any fractional crystallization, which was suspected to be the reason for the high optical purities in the work of Patel and Worsley. Indeed, optical purities obtained by Harada and Okawara were considerably lower (Table 4). The relationship between configuration of amine and product amino acid was found to hold, however.

The use of benzoyl cyanide as the source of cyanide for addition gave lower yields.²⁷ The use of a more sterically hindered amine, such as S-(-)- α -(1-naphthyl)-ethylamine, gave improvement only in the synthesis of valine.^{26,27}

Table 4. Addition of HCN to Schiff Bases of Aldehydes and α -Phenethylamines. Products Isolated as DNP Derivatives.

R in RCHO	Amine	Product	Yield %	Optical Purity
CH ₃ -	R(+)	R(-)-ala	54	40
CH ₃ -	S(-)	S(+)-ala	58	41
(CH ₃) ₂ CH-	R(+)	R(-)-val	21	31
(CH ₃) ₂ CHCH ₂ -	R(+)	R(-)-leu	40	24

Increases in optical purities have, however, been achieved by the use of cyanosilylation.²⁸ In the presence of a catalytic amount of a Lewis acid (e.g., ZnI₂), Schiff bases (again prepared with the chiral α -phenethylamines) undergo smooth addition of trimethylsilylcyanide (TMSCN). The intermediate **11** is hydrolyzed, and the silicon component removed in vacuo. Optical purities were determined at the nitrile stage, and found to be as high as 75%; furthermore, chemical yields to that stage are better than 97% (Table 5). Hydrolysis and hydrogenolysis would then give the α -amino acid.

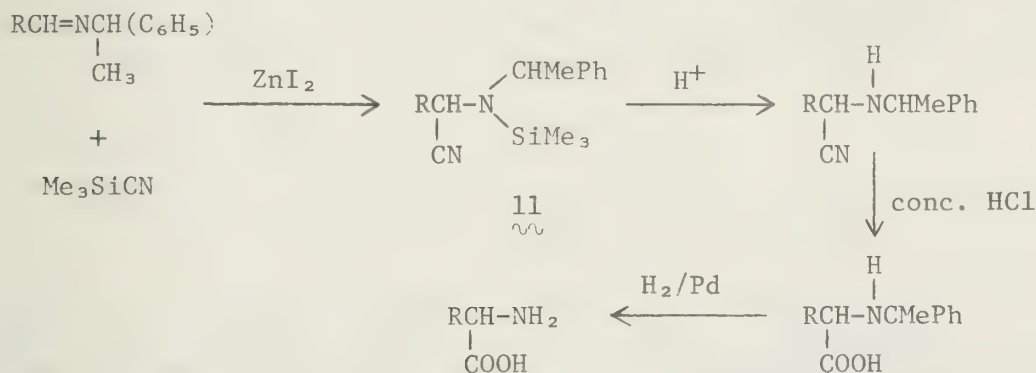
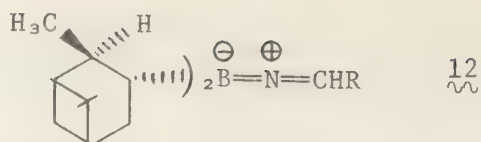


Table 5. Yields and Optical Purities of Methylbenzylaminonitriles Obtained by Cyanosilylation of Schiff Bases.

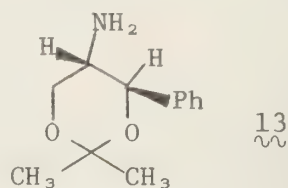
R in RCHO	Amino Acid Nitrile Is Precursor To	Yield %	Optical Purity
CH ₃ CH ₂ -	S-norvaline	97	63
CH ₃ CH ₂ CH ₂ -	S-norleucine	98.5	68
(CH ₃) ₂ CH ₂ -	S-valine	99.8	75
(CH ₃) ₂ CH ₂ CH ₂ -	S-leucine	97.5	61

In a novel approach to the addition of HCN to a C=N bond, Diner and coworkers prepared the ketiminoborane **12** from a chiral borane, diisopinocampheylborane, and an aliphatic nitrile. The ketiminoborane undergoes addition of HCN supplied by acetone cyanohydrin; alcoholysis followed by hydrolysis yields the amino acid hydrochloride. (S)-Valine (R = CH(CH₃)₂)

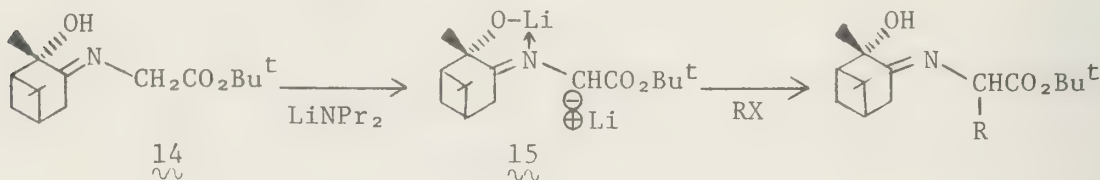
was prepared in 45% yield, with an optical purity of 12.4%.²⁹ Further investigation into this reaction has not yet been reported.



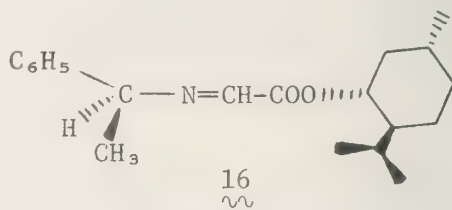
The synthesis of α -methyl α -amino acids in high (up to 100%) optical purities has been accomplished by the addition of cyanide ion to the Schiff bases formed from aliphatic or aromatic ketones and (4S;5S)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane 13, a chiral amine available in large quantities as an intermediate in the chloramphenicol synthesis. One product, (S)-3-(3,4-dihydroxyphenyl)-2-methylalanine (Methyl-dopa) is of medical importance as an anti-hypertensive agent.^{30,31}



In the previous examples, the carbon which is eventually the carboxylate moiety is introduced as the cyanide group. Yamada and coworkers have demonstrated that this is not the only approach that can be taken.³² They synthesized alanine, leucine, and phenylalanine by the alkylation of a chiral Schiff base formed from glycine *t*-butyl ester and (1S,2S,3S)-2-hydroxypinan-3-one (14). Treatment of the dilithio salt 15 with an alkyl or benzyl halide yielded the monoalkylated Schiff base, which was then hydrolyzed to yield the amino acid ester and regenerated chiral reagent. Optical purities were quite high: 72% for (S)-phenylalanine, and 83% for (S)-leucine and (S)-alanine, which chemical yields better than 50%,



Similarly, the alkylation of chiral Schiff bases with Grignard reagents has been reported by Fiaud and Kagan.³³ The Schiff bases 16 were prepared from α -phenethylamines and the (-)-menthyl ester of glycine. As the chirality of the product amino acids was in this case independent of the configuration of the amine, the directing influence was probably the menthyl ester portion of the molecules. By this method, S-alanine, S-valine, and S-phenylalanine were prepared in 38, 45, and 46% optical purities, respectively.



Miscellaneous Syntheses. Neber Rearrangement. The asymmetric synthesis of several α -amino acids has been approached through the use of a Neber rearrangement of (-)-menthyl N-chlorimidates.³⁴ Treatment of the chlorimide 17 with sodium ethoxide or potassium *t*-butoxide generates the resonance-stabilized intermediate 18, which undergoes cyclization to the aziridine. Addition of alcohol and hydrolysis with aqueous mineral acid yields the salt of the amino acid ester. This reaction sequence has been applied to the synthesis of both aryl and alkyl amino acids (Table 6). The asymmetric induction is due to the ester; in the cyclization to the aziridine, the

Chiral glycine molecules arise from deuterium or tritium substitution on the α -carbon. Armarego and coworkers³⁵ prepared (R)-(2-²H)- and (S)-(2-²H)-glycines in 80 and 92% optical purities, although their eight step synthesis from O-benzylserine proceeded in only 15% overall yield. Golding and coworkers³⁶ used a chiral complex of N-benzylglycine with bis(ethylene-diamine) cobalt (III) to stereospecifically exchange, in basic solution, one of the α -hydrogens, yielding (S)-N-benzyl-1-(2-²H)-glycine in approximately 80% optical purity.

The natural amino acid threonine exists in two forms, erythro- and threo-, but only the threo isomer is of value as a nutritional supplement. Matsumoto and coworkers³⁷ prepared threo-4,4,4-trichlorothreonine stereoselectively from the base-catalyzed condensation of chloral and 2-isocyanoacetate. Hydrogenation of the trichlorothreonine with H₂ and Pd/C gave threo-threonine in 95% yield, free of erythro-isomer. Later, the same workers³⁸ prepared threo-threonine in 85% optical purity by acid hydrolysis of a 5-methyl-4-alkoxycarbonyl-2-oxazoline formed from isocyanoacetate and acetaldehyde.

Valine has been prepared in 26% optical purity by Hayakawa and Shimizu by the stereospecific decarboxylation of α -(α -methylbenzylamino)- α -isopropylmalonic acid.³⁹ Alanine in 36% optical purity has been prepared by Okawara and Harada from (R) and (S)- α -methylbenzyl- β -bromopropionamides by conversion to a N,N'-bis(α -methylbenzyl)-piperazine-2,5-dione using sodium hydride, followed by hydrolysis and hydrogenolysis to give the free amino acid.⁴⁰

Finally, in an unusual approach to preparing amino acids in high optical purities, Clark and coworkers have reported the preparation of substituted phenylglycines in nearly 100% optical purities by stirring racemic mixtures of phenylglycines with (+)-tartaric acid in alcohols in the presence of carbonyl compounds. Extension to other amino acids may be limited, however, as (S)-methionine was recovered in only 58% optical purity.⁴¹ The reaction apparently works through facile racemization of optically active Schiff bases.

Conclusions. Several methods now exist for the synthesis of α -amino acids in high optical purities. Particularly notable are the catalytic hydrogenation of alkylidene and arylidene dioxopiperazines, and the reduction of α -acylaminoacrylic acids with soluble chiral rhodium catalysts. However, much work still needs to be done, both in the optimization of yields and the development of asymmetric approaches to the more complex amino acids, such as methionine, serine, tryptophan, cysteine, lysine, asparagine, and histidine.

BIBLIOGRAPHY

1. T. Kanako, Y. Izumi, I. Chibata, and T. Itoh, "Synthetic Production and Utilization of Amino Acids", Wiley and Sons, New York, N.Y., 1974.
2. J. B. Longernecker and E. E. Smith, Proc. Nat. Acad. Sci. U.S.A., 42, 221 (1956).
3. A. Thomson in "Organic Chemistry, Series One", D. H. Hey and D. I. John, eds., Vol. 6, University Park Press, Baltimore, Md., 1973.
4. E. A. Bell and D. I. John in "Organic Chemistry, Series Two", H. N. Rydon, ed., Vol. 6, Butterworths, Boston, 1976.
5. K. Weinges and B. Stemmler, "Asymmetric Synthesis of α -Amino Acids", Recent Dev. in the Chem. of Carbon Comp., Vol. VII, R. Bogner, V. Bruckner, and Cs. Czantay, eds., Akademiai Kiado, Budapest, 1976.

6. L. G. Dammann, Organic Chemistry Seminar, Univ. of Illinois, 1970, pp. 65-66.
7. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, New Jersey, 1971.
8. J. W. Scott and D. Valentine, *Science*, 184, 943 (1974).
9. R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956); *Angew. Chem.*, 78, 413 (1966).
10. E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Am. Chem. Soc.*, 92, 2476 (1970).
11. E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *J. Am. Chem. Soc.*, 92, 2488 (1970).
12. H. Poisel and U. Schmidt, *Chem. Ber.*, 106, 3408 (1973).
13. B. W. Bycroft, and C. R. Lee, *J. Chem. Soc., Chem. Commun.*, 988 (1975).
14. T.-P. Dang and H. B. Kagan, *J. Am. Chem. Soc.*, 94, 6429 (1972).
15. H. B. Kagan and T.-P. Dang, *J. Chem. Soc., Chem. Commun.*, 481 (1971).
16. W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Chem. Soc., Chem. Commun.*, 10 (1972).
17. W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem. Soc.*, 98, 2568 (1976).
18. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachmann, and D. J. Weinkauff, *J. Am. Chem. Soc.*, 99, 5946 (1977).
19. K. Achiwa, *J. Am. Chem. Soc.*, 98, 8266 (1976).
20. B. R. James, D. K. Wang, and R. F. Voight, *J. Chem. Soc., Chem. Commun.*, 574 (1975).
21. W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, U.S. Patent 4,935,127; C.A., 86;190463.
22. Y. Kawabata, M. Tanaka, and I. Ogata, *Chem. Lett.*, 1213 (1976).
23. (a) D. Hoppe and R. Follmann, *Chem. Ber.*, 109, 3062 (1976); (b) J. M. Riordan, M. Sato, and C. H. Stammer, *J. Org. Chem.*, 42, 236 (1977) and references therein.
24. G. Gelbard, H. B. Kagan, and R. Stern, *Tetrahedron*, 32, 233 (1976).
25. M. S. Patel and M. Worsley, *Can. J. Chem.*, 48, 1881 (1970).
26. K. Harada and T. Okawara, *J. Org. Chem.*, 38, 707 (1973).
27. K. Harada and T. Okawara, *Bull. Chem. Soc. Japan*, 46, 191 (1973).
28. I. Ojima and S. Inaba, *Chem. Lett.*, 737 (1975).
29. U. E. Diner, M. Worsely, J. W. Lown, and J.-D. Forsythe, *Tetrahedron Lett.*, 3145 (1972).
30. K. Weinges, G. Graab, D. Nagel, and B. Stemmle, *Chem. Ber.*, 104, 3594 (1971).
31. K. Weinges and B. Stemmle, *Chem. Ber.*, 106, 2291 (1973).
32. S. Yamada, T. Oguri, and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, 136 (1976).
33. J.-C. Fiaud and H. B. Kagan, *Tetrahedron Lett.*, 1019 (1971).
34. Y. Nogami, Y. Kawazue, and T. Taguchi, *Yakugaku Zasshi*, 93, 1058 (1973).
35. J. Y. Chenard, D. Commereuc, and Y. Chauvin, *J. Chem. Soc., Chem. Commun.*, 750 (1972).
36. W. L. Armarego, B. A. Milloy, and W. Pendergast, *J. Chem. Soc., Perkin I*, 2229 (1976).
37. B. T. Golding, G. J. Gainesford, A. J. Herlt, and A. M. Sargeson, *Tetrahedron*, 32, 389 (1976).
38. K. Matsumoto, Y. Urabe, Y. Ozaki, T. Iwasaki, and M. Miyoshi, *Agr. Biol. Chem. (Japan)*, 39, 1869 (1975).
39. K. Matsumoto, Y. Ozaki, M. Suzuki, and M. Miyoshi, *Agr. Biol. Chem. (Japan)*, 40, 2045 (1976).
40. T. Hayakawa and K. Shimizu, *Bull. Chem. Soc. Japan*, 46, 1886 (1973).
41. T. Okawara and K. Harada, *Bull. Chem. Soc. Japan*, 46, 1869 (1973).
42. J. C. Clark, G. H. Phillipps, and M. R. Steer, *J. Chem. Soc., Perkin I*, 475 (1976).

RECENT USES OF LITHIO DERIVATIVES OF OXIMES AND HYDRAZONES IN CARBON-CARBON BOND FORMING REACTIONS

Reported by Jerry D. Bryant

October 17, 1977

Hydrazones and oximes have long been used for derivatization-identification of organic compounds. Recently, the anions of hydrazones, arylhydrazones, dialkylhydrazones, tosylhydrazones and oximes have been recognized as valuable intermediates for a broad scope of synthetic reactions. This seminar will deal with the synthetic potential of these reagents and the interesting role of stereochemistry in the observed regioselectivity.

Hauser¹ first demonstrated the capacity of hydrazones for C α -alkylation through the formation of C-benzylated products from various C α ,N-dipotassio-phenylhydrazones (via KNH₂/NH₃). Later, C α ,N-dilithiophenylhydrazones and C α ,N,N-trilithiohydrazones were found to react with esters^{2,3} and nitriles⁴ to afford substituted pyrazoles upon acid workup. Phenylhydrazone dianions react with acid chlorides⁵ in an anomalous manner to yield 4-acylpyrazoles. The treatment of C α ,N-dilithiophenylhydrazones with aldehydes⁶ gives 2-pyrazolines upon acid cyclization. In the above studies, interest is primarily in novel heterocyclic syntheses rather than a possible method of α functionalization of carbonyls.

Dilithiooximes react with esters⁷ or nitriles⁴ to give, upon acid cyclization, substituted isoxazoles. Condensations have also been carried out using aldehydes, ketones and acid chlorides,⁸ CO₂⁹ and diethylxalate.¹⁰

Kofron¹¹ recognized and developed a method for regiospecific substitution of ketones via 1,4-dilithioketoximes, which undergo reaction with alkyl halides and carbonyl compounds.¹² The exclusive "syn" configuration of the dianion can be rationalized on the basis of chelation and an attractive non-bonded interaction in the 4 orbital, 6 π electron system.¹³ High stereoselectivity¹⁴ has been observed in reactions of the conformationally biased 4-*t*-butylcyclohexanone oxime. Similar regio-¹⁵ and stereoselectivity¹⁶ have been seen in reactions of ketone methoximes.

Shapiro¹⁷ recently reported a conversion of tosylhydrazones to alkenes¹⁸ utilizing alkyllithiums in a modified Bamford-Stevens reaction;¹⁹ however, the reaction was limited to olefin formation.²⁰ Recently, TMEDA was found to be the solvent of choice^{21,22} and the vinyl carbanion intermediate found to react with alkyl halides,²³ carbonyl compounds,²³ CO₂,²³ DMF²⁴ and trimethylsilyl chloride.^{25,26} Reaction occurs exclusively at what was the carbonyl carbon and the least substituted olefin is predominantly formed.²⁷ The reaction is limited to ketone arenesulfonylhydrazones.²⁸

Corey²⁹ and Stork³⁰ have utilized the metallated dimethylhydrazone (DMH) derivatives of "enolizable" aldehydes and ketones as synthetic equivalents of enolate anions. Through reaction with alkyl halides, aldehydes, ketones and epoxides, they obtained alkylated carbonyl compounds,²⁹ and β -hydroxy and γ -hydroxy³¹ carbonyl compounds, following mild oxidative²⁹ or cupric ion catalyzed³² hydrolysis. The aldehyde DMH anions react with trimethylsilyl chloride and the products are remetallated and treated with aldehydes and ketones to provide a simple route to α,β -unsaturated aldehydes.³³ Similar reactions have been run using polyfunctional DMH's.³⁴ Corey³⁵ also developed methodology utilizing α -methylthio DMH's as synthetic equivalents to acyl carbonium ions.

The DMH anion reactions display high regio- and stereoselectivity. Metallation of ketone DMH's occurs very selectively at the least alkylated carbon. Newcomb³⁶ suggests that a complete description of the selectivity of DMH anion reactions must include a description of the stereochemistry and relative population of the various intermediate DMH anions.

Enders has recently formed chiral hydrazones of ketones³⁷ and aldehydes.³⁸ Deprotonation and C α -alkylation then affords chiral aldehydes and ketones in good optical range and synthetic yield.

Quite recently, a ¹³C NMR technique for the rapid and unequivocal determination of the syn-anti stereochemistry of these derivatives has been developed.³⁹ It may be of value in improving the synthetic potential of these reagents.

BIBLIOGRAPHY

1. F. E. Henoch, K. G. Hampton, and C. R. Hauser, J. Am. Chem. Soc., 91, 676 (1969).
2. R. S. Foote, C. F. Beam, and C. R. Hauser, J. Heterocycl. Chem., 7, 589 (1970).
3. C. F. Beam and R. S. Foote, J. Chem. Soc. (C), 1658 (1971).
4. C. F. Beam, R. S. Foote, and C. R. Hauser, J. Heterocycl. Chem., 9, 183 (1972).
5. C. F. Beam, D. C. Reames, C. E. Harris, L. W. Dasher, W. M. Hollinger, N. L. Shealy, R. M. Sandifer, M. Perkins, and C. R. Hauser, J. Org. Chem., 40, 514 (1975).
6. D. C. Reames, C. E. Harris, L. W. Dasher, R. M. Sandifer, W. M. Hollinger, and C. F. Beam, J. Heterocycl. Chem., 12, 779 (1975).
7. C. F. Beam, M. C. Dyer, R. A. Schwarz, and C. R. Hauser, J. Org. Chem., 35, 1806 (1970).
8. R. M. Sandifer, S. E. Davis, and C. F. Beam, Synth. Commun., 6, 339 (1976); see ref. 11.
9. J. S. Griffiths, C. F. Beam, and C. R. Hauser, J. Chem. Soc. (C), 974 (1971).
10. R. M. Sandifer, L. W. Dasher, W. M. Hollinger, C. W. Thomas, D. C. Reames, C. F. Beam, R. S. Foote, and C. R. Hauser, J. Heterocycl. Chem., 12, 1159 (1975).
11. W. G. Kofron and M. K. Yeh, J. Org. Chem., 41, 439 (1976).
12. A mild method of ketone regeneration was recently reported; S. R. Maynez, L. Pelavin, and G. Erker, J. Org. Chem., 40, 3302 (1975).
13. M. E. Jung, P. A. Blair, and J. A. Lowe, Tetrahedron Lett., 1439 (1976).
14. R. E. Lyle, J. E. Saavedra, G. G. Lyle, H. M. Fribush, J. L. Marshall, W. Lijinsky, and G. M. Singer, Tetrahedron Lett., 4431 (1976).
15. T. A. Spencer and C. W. Leong, Tetrahedron Lett., 3889 (1975).
16. R. R. Fraser and K. L. Dhawan, J.C.S. Chem. Commun., 674 (1976).
17. R. H. Shapiro and M. J. Heath, J. Am. Chem. Soc., 89, 5734 (1967).
18. For a recent review see: Organic Reactions, 23, 405 (1976).
19. W. R. Bamford and T. S. Stevens, J. Chem. Soc., 4735 (1952).
20. R. H. Shapiro and E. C. Hornaman, J. Org. Chem., 39, 2302 (1974).
21. J. E. Stemke and F. T. Bond, Tetrahedron Lett., 1815 (1975).
22. R. H. Shapiro and L. A. Capuano, Tetrahedron Lett., 1811 (1975).
23. J. E. Stemke, A. R. Chamberlain, and F. T. Bond, Tetrahedron Lett., 2947 (1976).
24. P. C. Traas, H. Boelens, and H. J. Takken, Tetrahedron Lett., 2287 (1976).
25. T. H. Chan, A. Baldassaure, and D. Massuda, Synthesis, 801 (1976).

26. R. T. Taylor, C. R. Degenhardt, W. P. Melega, and L. A. Paquette, *Tetrahedron Lett.*, 159 (1977).
27. W. G. Dauben, G. T. Rivers, W. T. Zimmerman, N. Y. Yang, B. Kim, and J. Yang, *Tetrahedron Lett.*, 2951 (1976).
28. E. Vedjs and W. T. Stolle, *Tetrahedron Lett.*, 135 (1977).
29. E. J. Corey and D. Enders, *Tetrahedron Lett.*, 3 (1976).
30. G. Stork and J. Benaim, *J. Am. Chem. Soc.*, 93, 5938 (1971).
31. E. J. Corey and D. Enders, *Tetrahedron Lett.*, 11 (1976).
32. E. J. Corey and S. Knapp, *Tetrahedron Lett.*, 3667 (1976).
33. E. J. Corey, D. Enders, and M. G. Bock, *Tetrahedron Lett.*, 7 (1976).
34. T. Cuvigny and H. Normant, *Synthesis*, 198 (1977).
35. E. J. Corey and S. Knapp, *Tetrahedron Lett.*, 4687 (1976).
36. M. Newcomb and D. E. Bergbreiter, *J. Chem. Soc. Chem. Commun.*, 486 (1977).
37. D. Enders and H. Eichenauer, *Angew. Chem. Int. Ed. Engl.*, 15, 549 (1976).
38. D. Enders and H. Eichenauer, *Tetrahedron Lett.*, 191 (1977).
39. C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, 42, 2614 (1977).

RHODIUM-CATALYZED INTRAMOLECULAR REARRANGEMENTS

Reported by Pat Savu

October 20, 1977

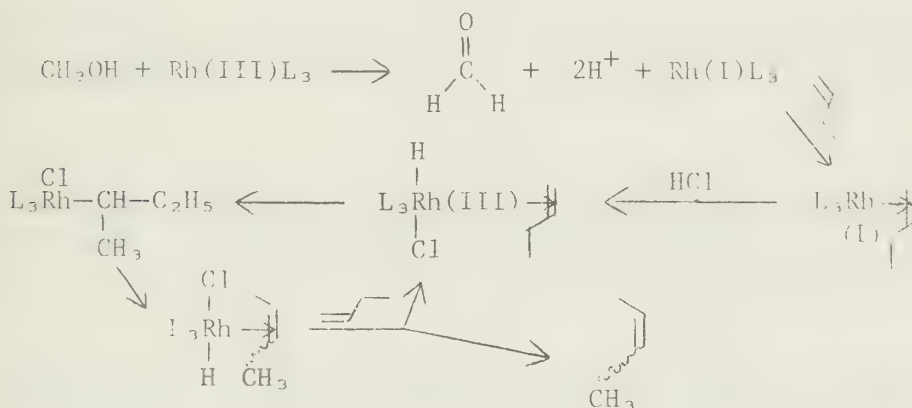
Introduction. Rhodium homogeneous catalysts are known to mediate a number of chemical processes. Probably the best known is hydrogenation. Rhodium also catalyzes a number of rearrangements in which there is no net change in the oxidation state of the rhodium or the organic substrate. Many of these reactions were discovered as side-reactions of the hydrogenation process.^{1,2} The two main categories of reactions catalyzed by rhodium are olefin isomerizations and rearrangements of strained ring compounds.

This seminar will discuss the scope and mechanism of rhodium-catalyzed intramolecular rearrangements and any possible synthetic utility they might have. Focus on rhodium is not as restrictive as it seems at first. Other transition metals effect similar conversions, such as nickel,^{1,10} silver,^{2,3} palladium,^{3,4,5,10} platinum,^{3,5,10} ruthenium,³ iridium,³ iron,^{4,10} and others; only the specific details differ.

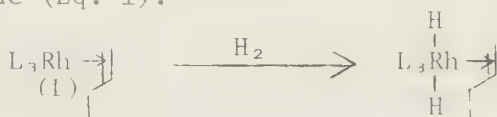
1. Olefin Isomerizations

Mechanism. Isomerization of 1-butene to 2-butene was discovered as a side-product in the dimerization of ethylene catalyzed by RhCl_3 . Up to 70% of the 1-butene formed was isomerized to 2-butene under the reaction conditions employed.⁷ Cramer^{9,10} later studied the mechanism of this process. He found that the isomerization was observable at -25°C , that a co-catalyst such as H_2 or HCl was necessary for an appreciable reaction, that if the reaction was done in deuterated methanol, approximately one deuterium atom was exchanged for each molecule of 1-butene that was isomerized, and that less than one percent of the butenes reisolated were di-deuterated. He proposed the following mechanism (Scheme I).

Scheme I

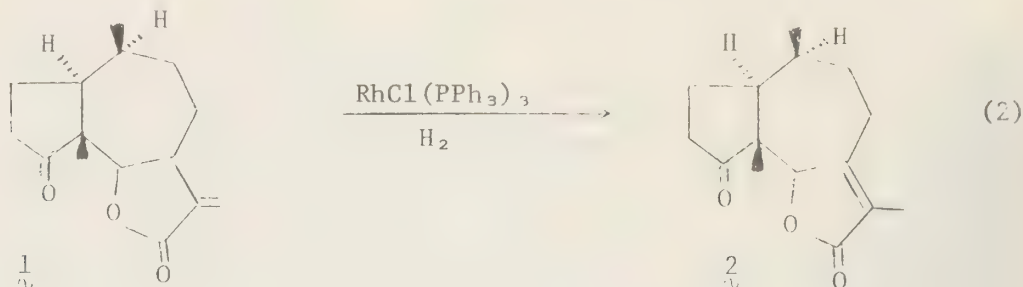


Facts relevant to Scheme I are that Rh(III) , which was used as $\text{RhCl}_3 \cdot \text{H}_2\text{O}$, can be reduced in alcoholic solvents to its I state,¹¹ and that Rh(I) or Rh(III) can form a π -olefin complex when mixed with olefins.⁹ The co-catalyst HCl oxidatively adds to the rhodium(I) complexed olefin to form a rhodium(III) hydride complexed olefin. Hydrogen can act similarly to form a dihydride (Eq. 1).



(1)

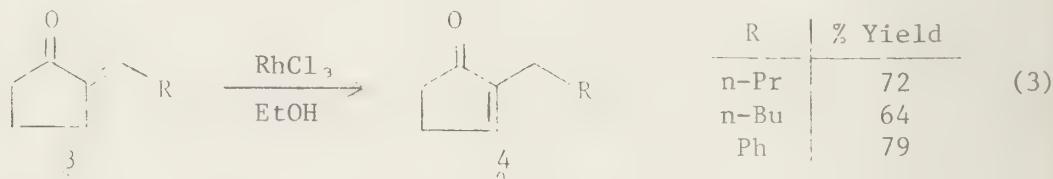
Biellman and Jung¹² proposed a similar mechanism for the rhodium-catalyzed isomerization of damsine (1) to isodamsine (2).



Use of one equivalent of D_2 led to incorporation of deuterium into 2 in 58% yield. No dideuterated isodamsine was isolated. The reason that not quite one deuterium was transferred for every molecule of isodamsine produced is because $RhClD_2(PPh_3)_2$ (olefin) is progressively replaced by $RhClHP(PPh_3)_2$ (olefin) and $RhClH_2(PPh_3)_2$ (olefin) as the reaction nears completion. No reaction occurred in the absence of hydrogen.

Recently, other workers^{14,21,22} have found that a co-catalyst is not required. However, Cramer performed his experiments at 0° . It is possible that at the elevated temperatures at which the others performed their experiments, the acid produced by the reduction of Rh(III) to Rh(I) was sufficient to generate the Rh(III) hydride and cause isomerization.

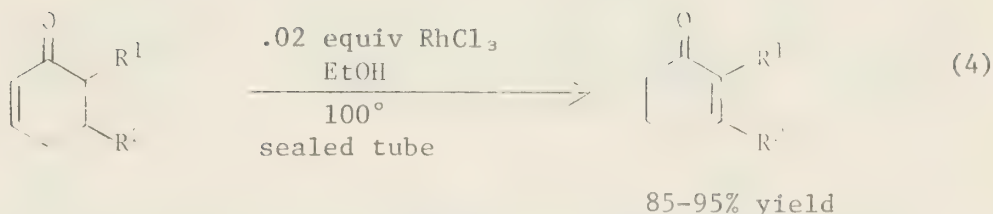
Synthetically Useful Rh Transformations. Compounds of type 3 are useful intermediates in the synthesis of natural products, but are difficult to prepare.¹³



Patin and co-workers¹⁴ have prepared these compounds in high yields from compound type 3 using $RhCl_3 \cdot 3H_2O$ in refluxing ethanol. This type of rearrangement is known also to be caused by acid alone, but yields are lower.¹⁵

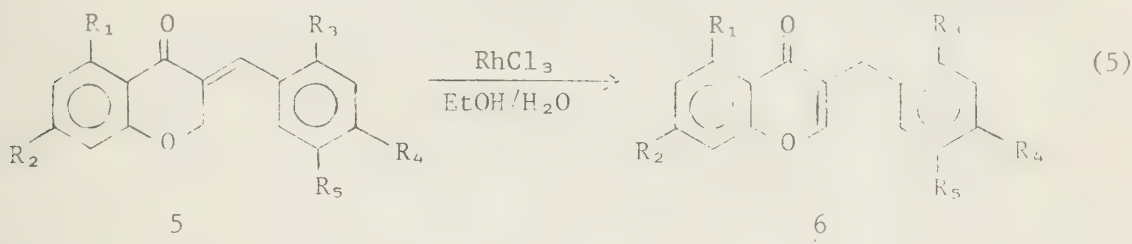
Double bond movement within cyclopentenones to form the most substituted olefin in conjugation with the carbonyl are well known to be catalyzed by acid¹⁶ or base.¹⁷ Double bond migrations in larger rings are often difficult to effect; rather harsh conditions are necessary.^{18,19,20} Birch and Subba Rao,²¹ however, found that simple and complex 1-methoxy-1,4-dienes in cyclohexane ring systems when refluxed with 1% by weight tris(triphenylphosphine)rhodium chloride in chloroform for two hours rearranged cleanly to 1-methoxy-1,3-dienes even when the ring was part of a steroid.

Except in the case of cyclopentenones, there is only one other recorded^{18,22} isomerization of the least substituted α,β -unsaturated cycloalkenone to its most substituted α,β -unsaturated isomer catalyzed by acid or base. Grieco and co-workers²² have employed $RhCl_3$ in ethanol to bring about this transformation in cyclohexenones (Eq. 4).



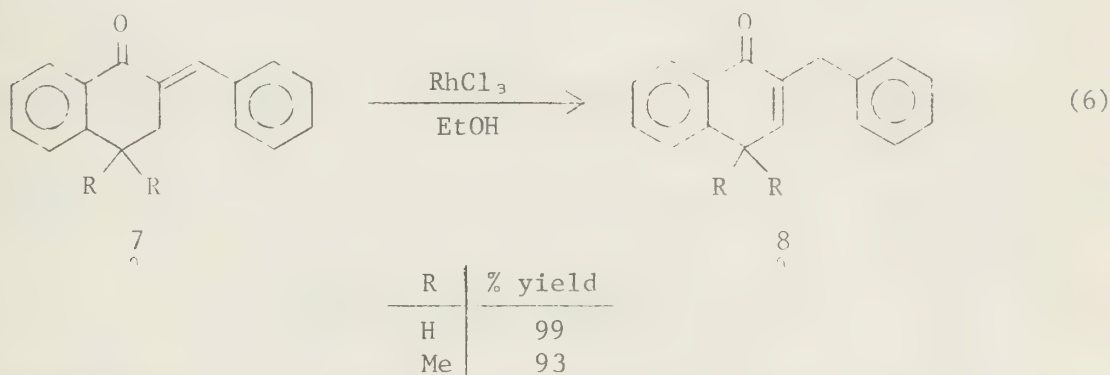
The corresponding migration in ring sizes seven and nine were also carried out;²² 7-n-butyl-cyclohept-2-en-1-one and 9-n-butyl-cyclonon-2-en-1-one were isomerized to 2-n-butyl-cyclohept-2-en-1-one and 2-n-butyl-cyclonon-2-en-1-one in 80 and 88% yield, respectively. In all three cases, six, seven, and nine membered rings, the only other compounds present in the reaction mixture at the end were 4-6% of the corresponding saturated ketones.

Rhodium catalysts have also been used in the synthesis of more complex molecules. Homoisoflavones (6) can be synthesized from readily obtainable arylmethylenechroman-4-ones (5) in nearly quantitative yield for $R_1 = R_2 = R_3 = R_4 = R_5 = H$; $R_1 = R_2 = H$, $R_3 = R_4 = R_5 = OMe$; and $R_1 = Me$, $R_2 = R_3 = R_4 = R_5 = OMe$ (Eq. 5).¹⁴

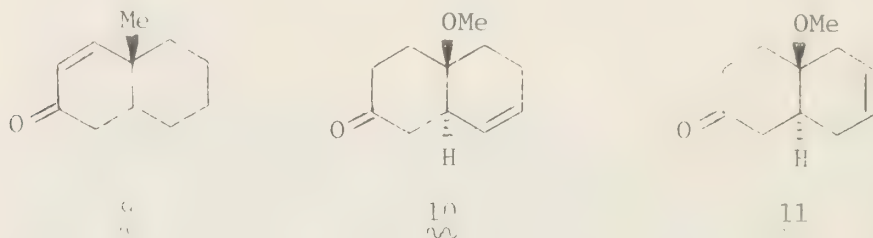


Without a catalyst, these isomerizations cannot be cleanly effected. They are degraded by base and unreactive towards acid. The homoisoflavone nucleus must otherwise be built up from dihydrochalcones and formate esters.²³

Compounds of type 8, previously obtainable only by a three step synthesis from 7 in 67% overall yield²⁴ can be directly synthesized from 7 through isomerization by $RhCl_3$ in refluxing ethanol.

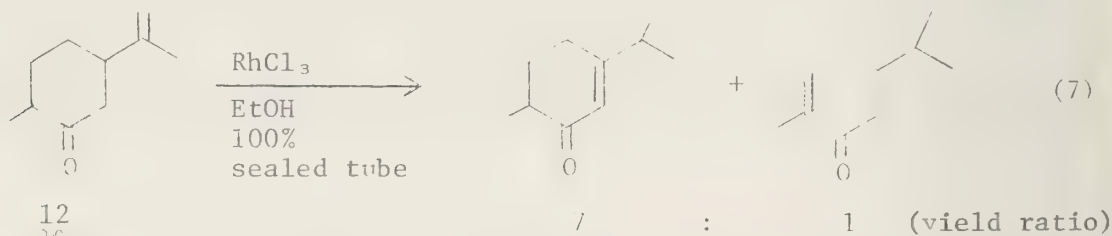


Limitations of Method. In cyclic systems, one of the limitations of rhodium-catalyzed isomerization is that there cannot be a quaternary center between the original position of the double bond and its desired final position. Compound 9 will not react at all and compound 10 yields compound 11 after treatment with RhCl_3 .²²

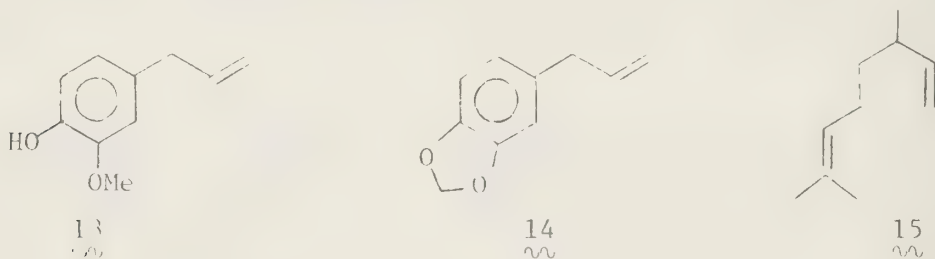


Probably, the double bond migrates around the ring and cannot move past any center that cannot become olefinic by loss of a hydrogen.

When the double bond is not part of a cyclic system, more often than not mixtures of products are obtained. This probably is due to only small differences in the energy between each of the potential products. Reaction of dihydrocarvone (12) with RhCl_3 leads to both possible α,β -unsaturated ketones, in a ratio of 7:1 in a yield of 90%.²²

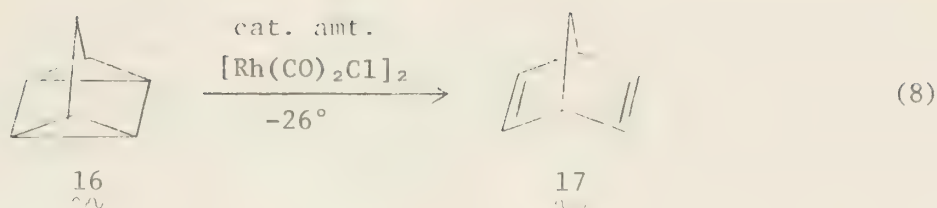


Eugenol (13), saffrole (14), and 3,7-dimethylocta-1,6-diene (15) give cis-trans mixtures of their isomers derived by moving their singly-substituted double bond over one carbon. The ratio of cis:trans for isoeugenol and isosaffrole is 10:90 and 20:80, respectively,¹⁴ and for 3,7-dimethylocta-2,6-diene the ratio of E:Z is 82:18.²⁵



2. Rhodium-Catalyzed Isomerization of Strained Ring Compounds

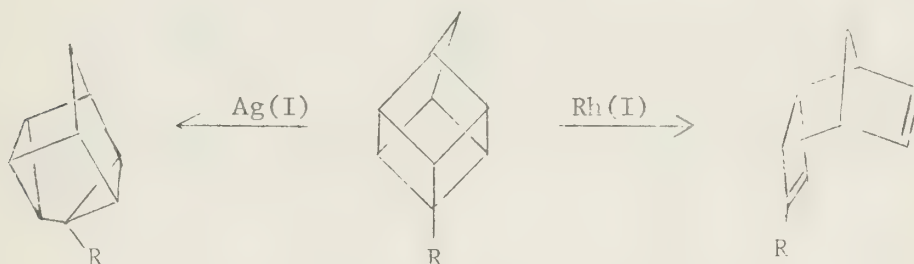
Mechanism. Quadricyclene (16) was one of the first molecules to be isomerized by a rhodium catalyst (Eq. 8).



Quadricyclene does rearrange to norbornadiene without catalyst; adding rhodium catalyst decreased its half-life from 14 hours at 140° to 45 min. at -26°C.²⁶

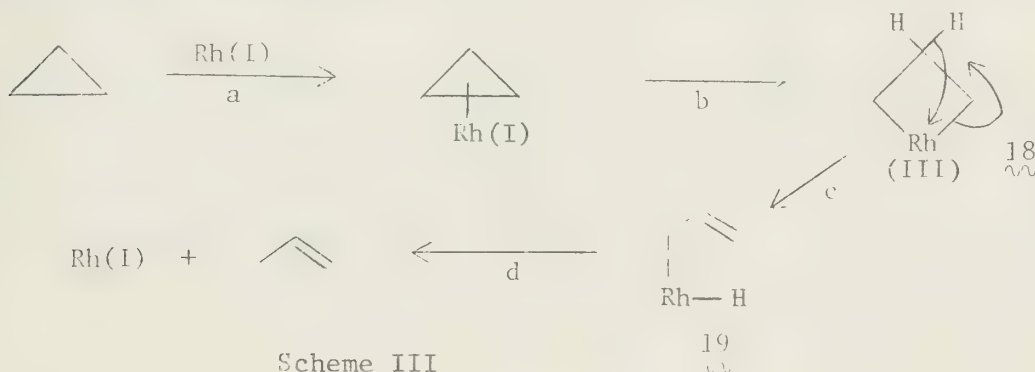
At first it was not known whether the mechanism of this type of rearrangement was concerted or step-wise. It had been found that cyclopropanes, cyclobutanes, epoxides, oxetans, and oxepins rearranged into ring-opened isomers. Conjugation of the small ring with a vinyl group^{27,28} or phenyl group^{27,28} or added strain within the molecule²⁹ increased the rate of reaction. The reaction had been found to be pseudo-zero order in organic substrate at small constant catalyst concentration (at a mole ratio of substrate to catalyst of more than 100:1);^{27,29} at larger catalyst concentrations, the reaction was found to be first order in organic substrate.^{26,27,30} Paquette and co-workers³ found the ρ^* value for ring opening of cyclobutyl ring in substituted homocubanes to be -0.87. The ρ^* value for silver-catalyzed rearrangement of the same substituted homocubanes to snoutane products was -2.33.

Scheme II



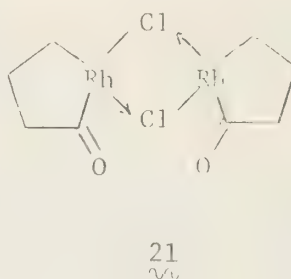
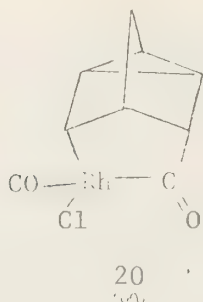
A small negative (-0.72) value was also found for the rhodium-catalyzed rearrangements of cubane, carboxycubane, and 1,4-bis(carboxycubane).^{3,30} This indicates that a full positive charge probably does not form in the rate-determining step.

The following scheme could accommodate these facts:



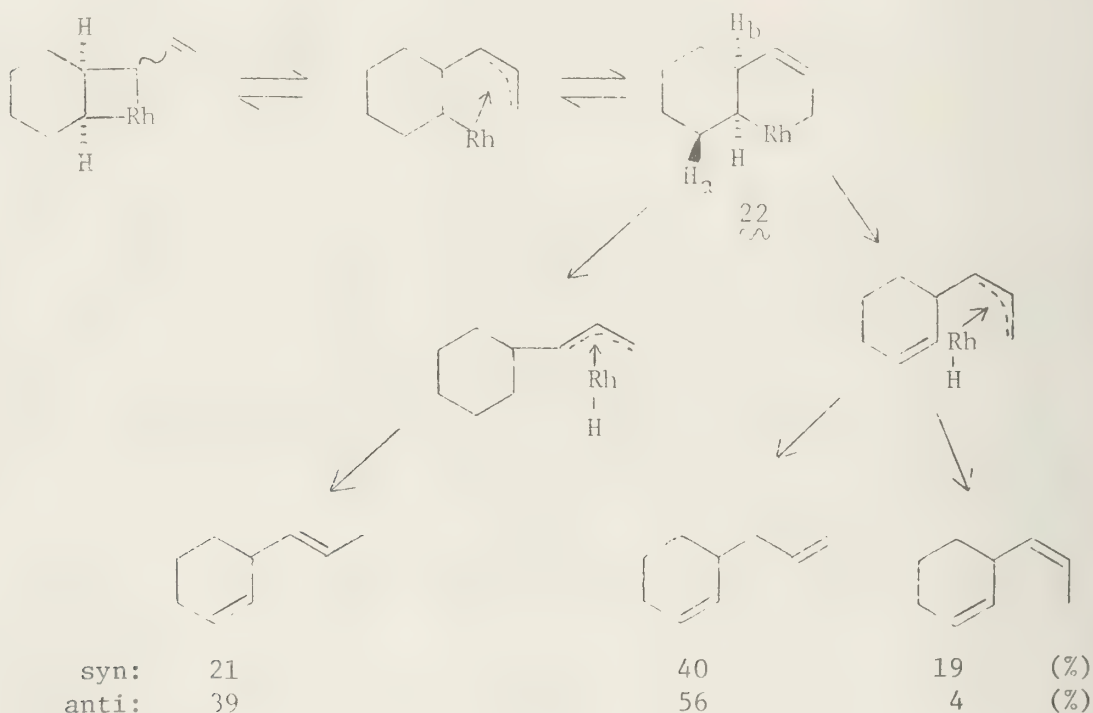
Scheme III

At very low catalyst concentrations virtually all the rhodium is complexed by the small ring or some pi system within the molecule, and the rate-determining step is b. Isolation of rhodium metallocenes support this mechanism. Compound 20 can be isolated if quadricyclene (16) is mixed with a stoichiometric amount of rhodium dicarbonyl dimer.³¹ Reaction of cyclopropane with an excess of rhodium dicarbonyl dimer yielded compound 21.³²



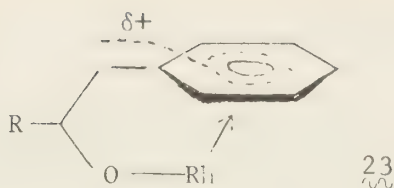
These compounds result when intermediate 18 breaks down by inserting one of its carbon monoxides in order to return to its +1 state.

Vinyl and phenyl cyclopropanes react more readily with the rhodium catalysts because for them there is an alternate mode of breakdown for compound 18. Salomon and Salomon²⁹ have proposed the following (Scheme IV) for the breakdown of 18 in the case of syn- or anti-7-vinylbicyclo[4.1.0]-heptane:



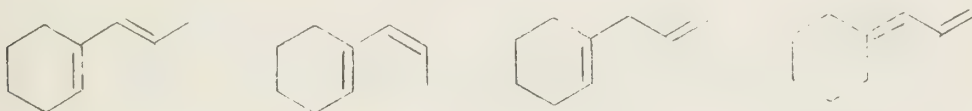
Scheme IV

A similar scheme could be drawn for the breakdown of phenyl cyclopropanes involving intermediate 23, analogous to compound 22, involving a complexed delocalized benzyl cation.



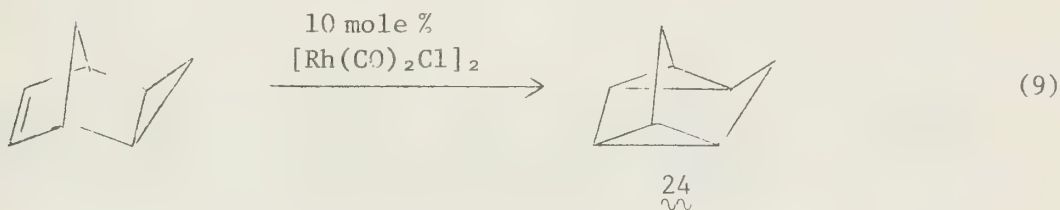
A similar mechanism has been proposed for the rearrangement of epoxides.³³ Blum and co-workers³⁴ claim that oxidative addition of the rhodium to the cyclopropyl ring will not explain their results in the rearrangement of substituted stilbene oxides to deoxybenzoins. They propose instead oxidative addition of the metal to an oxirane C-H bond. In fact, an intermediate of type 23 might also explain their data.

Both syn- and anti-7-vinylbicyclo-[4.1.0]-heptane yield the same products when isomerized by rhodium(I) to opened ring compounds. Neither yields any of the four possible compounds below:



The reason for this is the requirement for syn periplanar geometry for β hydride elimination.^{29,35} Only abstraction of H_a and not H_b in intermediate 22 can fulfill this requirement.

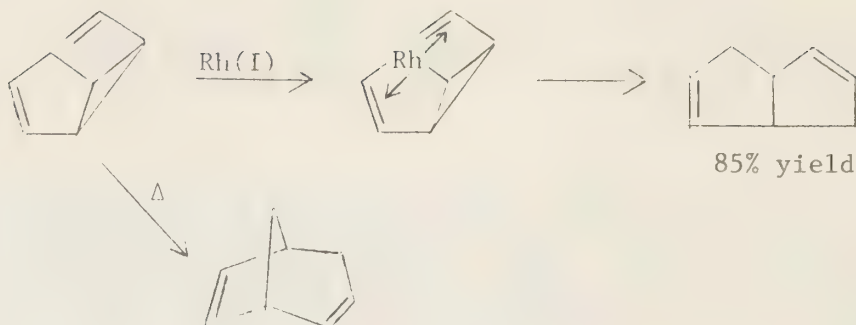
Scope and Potential Utility. Rhodium-catalyzed openings of strained rings are probably more interesting than synthetically useful. They have nevertheless been used to make a number of bicyclic compounds from other more readily available compounds.^{36,37} One interesting example of this involves a rearrangement in which one ring is opened while two other within the molecule are closed (Eq. 9).



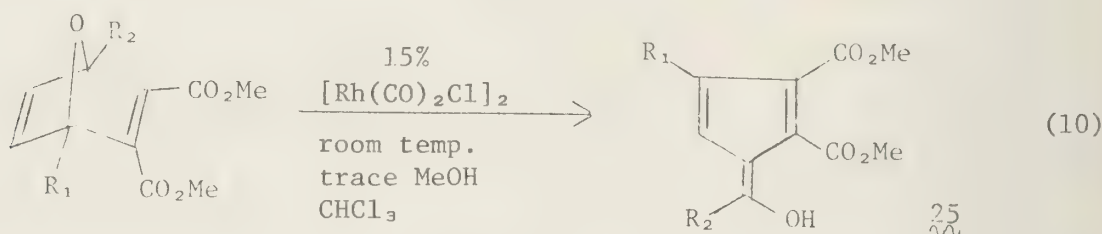
Product 24 is isolated in quantitative yield; thermal rearrangement yields none of 24.³⁸

Cyclopentenenes can also be synthesized from appropriate starting materials. The thermally allowed conversion of bicyclo[6.1.0]nonatriene into cis-8,9-dihydroindene can be done under milder conditions and more rapidly with rhodium(I) catalysts present.³⁹ Rhodium(I) can also catalyze thermally forbidden conversions (Scheme V).⁴⁰

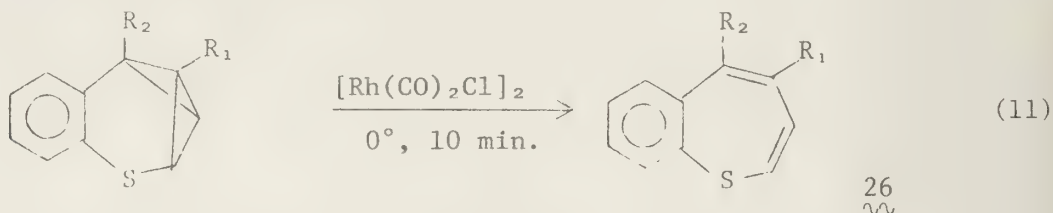
Scheme V



Six-hydroxyfulvenes (25) have been synthesized by the ring opening of oxanorbornadiene (Eq. 10) or oxaquadricyclene in greater than 90% yield for $R_1 = R_2 = \text{CH}_3$ or $R_1 = \text{H}$, $R_2 = \text{CH}_3$.^{41,42}



Rhodium(I) catalysts have been used in the synthesis of thermally labile 1-benzothiepins (26 in Eq. 12). For $R_2 = \text{H}$ or Me and $R_1 = \text{H}$ or Me yields are 98%.



Syntheses of 4-methoxycarbonyl and 4-formyl-1-benzothiepins were similarly effected.⁴³ Due to rapid expulsion of sulfur, 1-benzothiepins are thermally unstable and very difficult to synthesize. This was the first report of their successful synthesis.

Summary. Both rhodium-catalyzed olefin isomerizations and strained ring openings involve alkylrhodium(III) species. Conditions are usually mild, especially compared with comparable uncatalyzed cases.

BIBLIOGRAPHY

1. R. C. Miller and P. A. Pinke, J. Am. Chem. Soc., 90, 4500 (1968).
2. L. Cassar, P. E. Eaton, and J. Halpern, *ibid.*, 92, 6366 (1970).
3. L. A. Paquette, R. A. Boggs, and J. S. Ward, *ibid.*, 97, 1118 (1975).
4. G. Albelo, G. Wiger, and M. F. Rettig, *ibid.*, 97, 4510 (1975).
5. A. Bruggink and H. Hogeveen, Tetrahedron Lett., 4961 (1972).
6. Y. Takegami, Y. Watanbe, T. Mitsudo, and H. Masada, Bull. Chem. Soc. Japan, 42, 202 (1969).

7. T. Alderson, E. L. Jenner, and R. V. Linsey, Jr., J. Am. Chem. Soc., 87, 5638 (1965).
8. R. Cramer, *ibid.*, 88, 2272 (1966).
9. R. Cramer, Acc. Chem. Res., 1, 187 (1965).
10. R. Cramer and R. V. Lindsey, Jr., J. Am. Chem. Soc., 88, 3534 (1966).
11. J. Chatt and L. M. Venanzi, J. Chem. Soc., 4735 (1957).
12. J. F. Biellmann and M. J. Jung, J. Am. Chem. Soc., 90, 1673 (1968).
13. M. F. Ansell and W. Ducker, J. Chem. Soc., 329 (1959).
14. J. Andrieux, D. H. R. Barto, and H. Patin, J. Chem. Soc., Perkin I, 359 (1977).
15. J. M. Conia and J. Amice, Bull. Soc. Chim. France, 3329 (1968).
16. G. W. Caviel, B. S. Goodrich, and D. O. Lain, Austr. J. Chem., 23, 83 (1970).
17. G. Stork, G. L. Nelson, F. Rovessac, and O. Gringore, J. Am. Chem. Soc., 93, 3091 (1971).
18. H. O. House and R. W. Bashe, III, J. Org. Chem., 30, 2942 (1965).
19. A. J. Birch, J. Chem. Soc., 1642 (1947); A. J. Birch, Austr. J. Chem., 8, 96 (1955).
20. A. Schriesheim, J. E. Hoffman, and C. A. Rowe, Jr., J. Am. Chem. Soc., 83, 3731 (1961).
21. A. J. Birch and G. S. R. Subba Rao, Tetrahedron Lett., 3797 (1968).
22. P. A. Greico, M. Nishizawa, and N. Marinovic, J. Am. Chem. Soc., 98, 7102 (1976).
23. L. Farkas, A. Gottseger, M. Nogradi, and J. Strelisky, Tetrahedron, 27, 5049 (1971).
24. A. Hassner and N. H. Cromwell, J. Am. Chem. Soc., 80, 893 (1958).
25. F. J. McQuillin and D. G. Parker, J. Chem. Soc., Perkin I, 2092 (1975).
26. H. Hogeveen and H. C. Volger, J. Am. Chem. Soc., 89, 2486 (1967).
27. P. W. Chum and J. A. Roth, J. of Catalysis, 39, 198 (1975).
28. H. W. Vogt and J. A. Roth, J. of Catalysis, 33, 91 (1974).
29. R. G. Saloman and M. F. Salomon, J. C. Kachiniski, J. Am. Chem. Soc., 99, 1044 (1977).
30. L. Cassar, P. E. Eaton, and J. Halpern, *ibid.*, 92, 3515 (1970).
31. L. Cassar and J. Halpern, Chem. Commun., 1082 (1970).
32. D. M. Roundhill, D. N. Lawson, and G. Wilkinson, J. Chem. Soc. A, 845 (1968).
33. R. W. Ashworth and G. A. Berchtold, Tetrahedron Lett., 343 (1977).
34. D. M. Milstein, O. Buchman, and J. Blum, J. Org. Chem., 42, 2299 (1977).
35. T. J. Katz and S. A. Cerefice, J. Am. Chem. Soc., 93, 1049 (1971).
36. T. J. Katz and S. A. Cerefice, Tetrahedron Lett., 2509 (1969).
37. T. J. Katz and S. A. Cerefice, *ibid.*, 2561 (1969).
38. H. C. Volger, H. Hogeveen, and M. M. P. Gaasbeek, J. Am. Chem. Soc., 91, 218 (1969).
39. R. Grigg and R. Hayes, Chem. Commun., 1248 (1971).
40. V. Avis, T. M. Browne, J. A. Connedy, B. T. Golding, and R. H. Williamson, J. Chem. Soc., Perkin II, 4 (1975).
41. A. Brugink and H. Hogeveen, Tetrahedron Lett., 4961 (1972).
42. R. Roulet, J. Wenger, M. Hardy, and P. Vogel, Tetrahedron Lett., 1479 (1974).
43. I. Murata and T. Tatsuoka, *ibid.*, 2697 (1975).

TRANSITION METAL MEDIATED ALKYNE CYCLIZATIONS:
SYNTHETIC ASPECTS

Reported by Grant A. Krafft

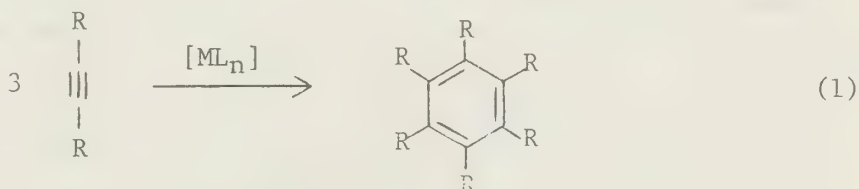
October 24, 1977

The construction of cyclic systems which contain a desired stereochemistry and specified substituent regiochemistry presents a significant challenge to the synthetic organic chemist. While conventional methods, such as Diels-Alder, aldol or Claisen reactions have been used extensively in the construction of ring systems, these methods often require numerous steps, thereby affording the target cyclic compounds in poor yield. Often, sensitive functional moieties cannot withstand harsh conditions (temperature, acid, base) usually required for such cyclization reactions. In many instances, target compounds contain substituted benzenoid systems, and must be synthesized from aromatic precursors via tedious aromatic functionalization schemes.

Acetylene cyclizations, mediated by transition metals, offer an alternative synthetic route to a wide variety of cyclic compounds. In many cases, this method offers the advantages of good yields, product specificity, functional group compatibility and substituent versatility.¹ Relatively complex structures can be obtained in a few synthetic steps when such a reaction is incorporated into the synthetic scheme.

The first occurrence of a transition metal mediated alkyne cyclization was reported in 1948 by Reppe *et al.*² It was observed that acetylene underwent cyclization to benzene, cyclooctatetraene or styrene in the presence of Ni(II) catalysts. While the oligomerization of acetylene had been observed as early as 1866,³ extreme reaction temperatures (300-400°C) and complex product mixture frustrated many early attempts to exploit this type of reaction in synthetic endeavors. Since 1949, extensive investigations of these transition metal mediated alkyne cyclizations have refined the reaction to a point where it is now a powerful tool in complex synthetic sequences.¹

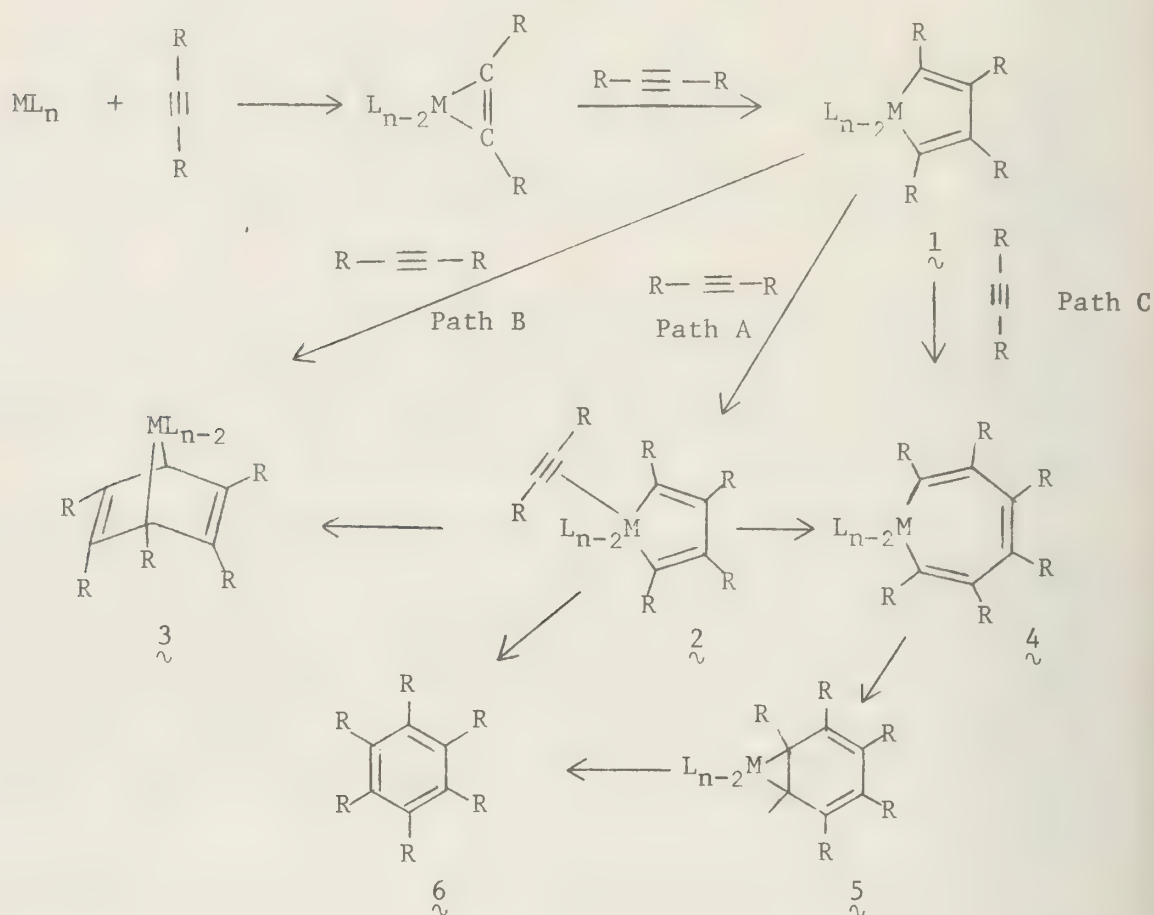
The trimerization of acetylenes (Eq. 1) proceeds with remarkable ease in the presence of transition metal catalysts, and indeed, numerous substituted benzenes have been prepared by this method.⁴⁻⁸ Typical conditions for these trimerizations consist of refluxing the acetylenes in benzene or toluene in the presence of 5 to 10 mole percent of the metal complex catalysts. Depending upon the catalyst and starting acetylene, regioselectivity has been achieved for 1,2,4-trisubstituted benzenes^{9,12,13,14} and 1,3,5-trisubstituted benzenes.⁹⁻¹¹ Numerous hexasubstituted benzenes have also been synthesized from disubstituted acetylenes.^{4,5,15}



Although the trimerization of alkynes to benzenes by transition metals has been well studied, unequivocal elucidation of the reaction mechanism has been difficult. Metallo-cyclobutadienoid complexes had been implicated

as reaction intermediates;^{16,17} however, work by several investigators^{18,19,33} has demonstrated these cyclobutadienoid complexes to be the result of side reactions, thereby refuting their role in the formation of substituted benzenes. A more plausible mechanism (Scheme I) has been proposed by Vollhardt^{1,20} and others²¹⁻²⁵ for the trimerization of alkynes with cobalt, nickel, rhodium, iridium and palladium catalysts. A metallo-cyclopentadiene

Scheme I

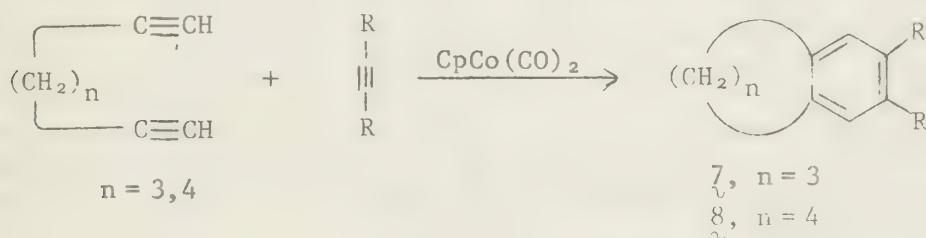


species, **1**, has been implicated as an intermediate in the reaction. Several of these intermediates have been isolated²⁰⁻²⁵ and shown to react with acetylenes to give substituted benzenoid products. These intermediates have also been shown to act as true catalysts in the trimerization reaction.^{24,26} The intermediate **1** (Scheme I) may react via paths A, B, or C to form **2**, **3**, or **4**, respectively, eventually leading to the benzenoid product, **6**.¹ It is difficult to determine the immediate fate of the metallo-cyclopentadiene, **1**, and it is entirely plausible that multiple pathways are involved. Path B involves an electrocyclic addition of the free alkyne to the metallo-cyclopentadiene, while path C requires insertion of the alkyne into the metal-carbon bond. It is more likely, however, that the free alkyne coordinates with the metal atom via path A, to form the transitory intermediate, **2**. Such complexation may afford stabilization in the transition state and provide a favorable configuration for the formation of the benzenoid, **6**.¹ Attempts are underway in several laboratories^{27,28} to detect the intermediates **2-5**, which will offer additional insight into the mechanism of this reaction.

From a synthetic viewpoint, the trimerization of acetylenes to form substituted benzenes is of limited synthetic utility. The extension of this reaction to elaborated alkynyl systems by Müller, Vollhardt and others, however, has opened the way for its use in efficient novel synthetic endeavors.²⁹⁻³¹

Synthesis of Indans, Tetralins and Anthraquinones. The cooligomerization of 1,6-heptadiyne and 1,7-octadiyne with substituted monoacetylenes, catalyzed by commercially available cyclopentadienyl dicarbonyl cobalt ($\text{CpCo}(\text{CO})_2$), has provided a synthetic entry into indans and tetralins, with essential control of aromatic substitution^{32,33} (Scheme II).

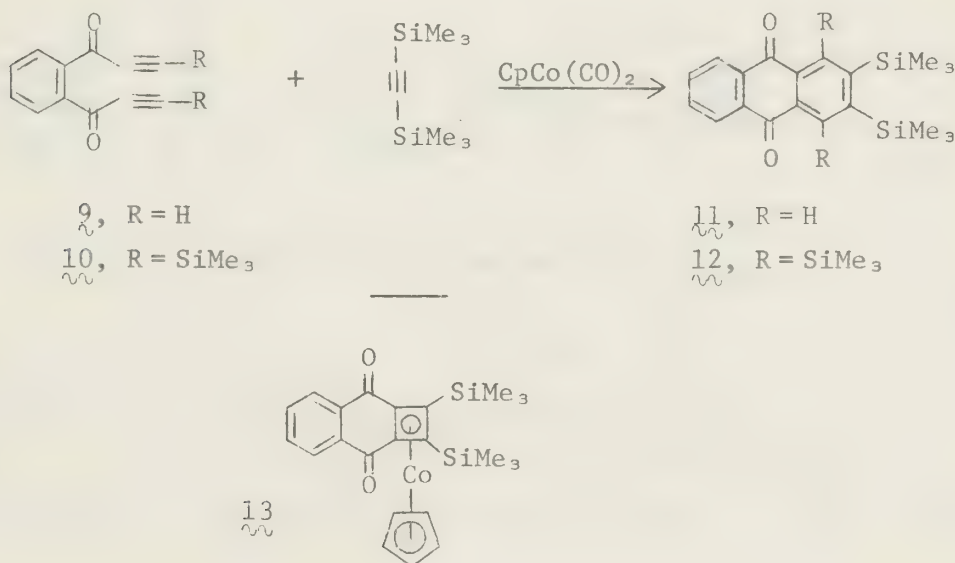
Scheme II



Side products stemming from the trimerization of the monoacetylenes and formation of complex cooligomers have led to low yields (20-35%) of the desired indans and tetralins, for many of the monoacetylenes that have been used. The use of bis-trimethylsilylacetylene (BTMSA) as the monoacetylene, however, has resulted in a high yield (80-85%) entry in this series, and provided a ready handle for subsequent elaboration of the aromatic ring.³³

The analogous catalytic sequence utilizing an α, α' -diketodiyne resulted in low yield (20-30%) production of anthraquinones³³ (Scheme III). Formation of stable cyclobutadiene-cobalt complexes, such as **13**, and instability of the starting diketodiyne were responsible for the low yields.

Scheme III



Müller succeeded in synthesizing various anthraquinones via a stoichiometric reaction, utilizing nickel, rhodium and iridium complexes^{21,29,34-37} (Scheme IV). Formation of the metal complexes was quantitative in most cases,^{21,37} with the overall yields of anthraquinones determined by steric and electronic properties of the substituted acetylenes. Numerous other complexes (Figure 1)^{34,38-41} were prepared and treated with various acetylenes to give a variety of interesting compounds (Figure 2)^{34,37-40} in good to excellent yields. Such metallo-cyclopentadiene complexes also have been treated with molecular oxygen, sulfur, selenium and carbon monoxide to give the corresponding furo-, thieno-, selenophenoisoindolequinones³⁸ and cyclopentadienone⁴² derivatives, respectively (Figure 3), in moderate to excellent yields. This synthetic route to anthraquinones may prove extremely useful in the synthesis of anthracycline antibiotics⁴³ such as daunorubicin,⁴⁴ adriamycin⁴⁵ and carminomycin⁴⁶ (Figure 4).

Scheme IV

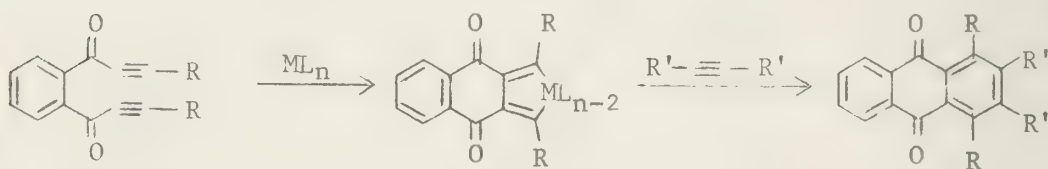


Figure 1. Metallocyclopentadiene intermediates in polycyclic syntheses

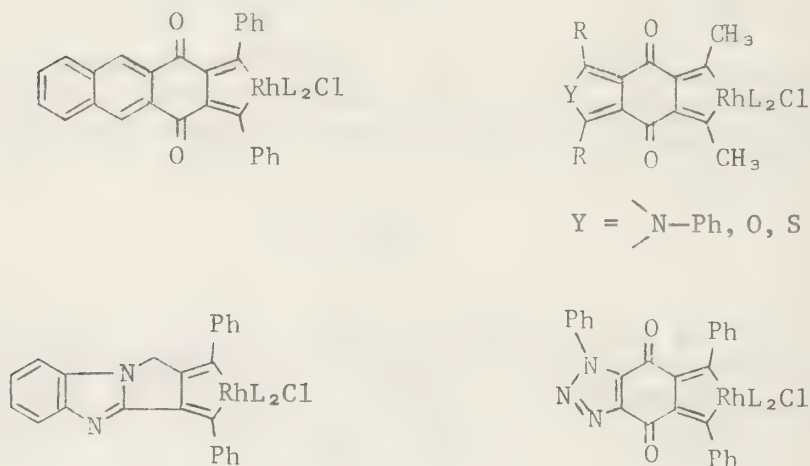


Figure 2. Anthra- and Naphthaquinone derivatives

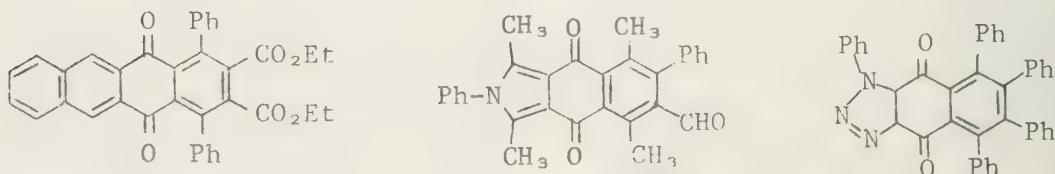
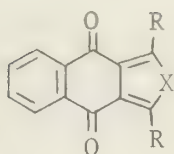
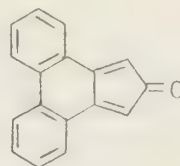


Figure 3. Other polycyclic derivatives

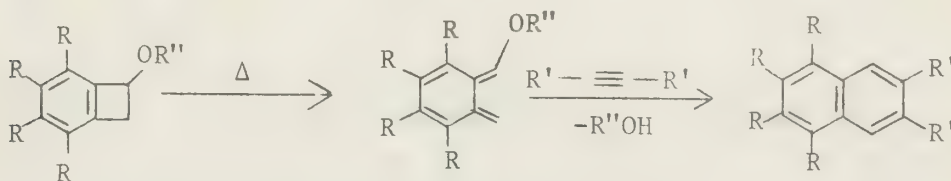


X = O, S, Se



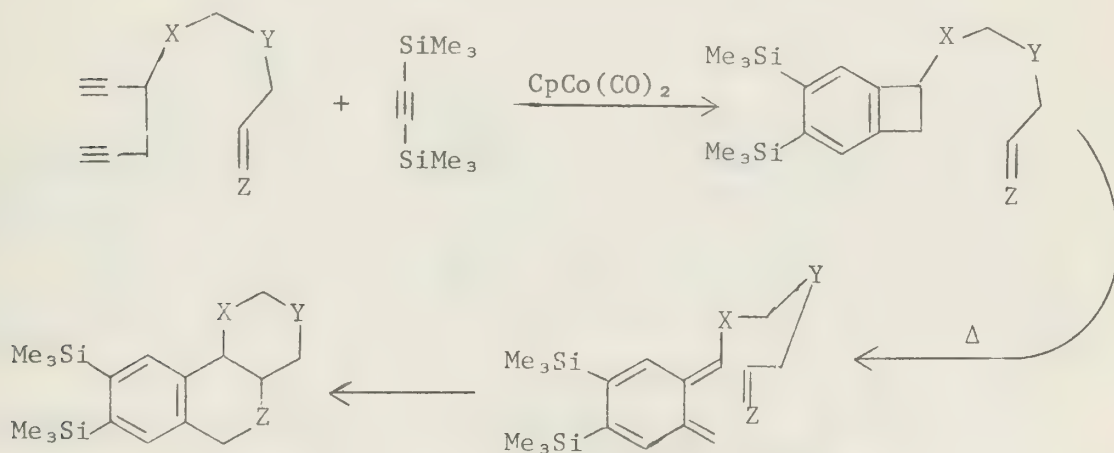
Synthesis of Benzocyclobutenes. When the α,ω -diacetylene 1,5-hexadiyne is treated with the catalyst cyclopentadienyldicarbonyl cobalt in the presence of monoacetylenes, benzocyclobutenes are formed in fair to good yield (Scheme II, $n = 2$).^{20,33} Formation of side products resulting from thermal ring opening of the cyclobutene ring diminishes the isolated yields of the benzocyclobutenes. Indeed, optimization of this side reaction has resulted in the synthesis of various substituted naphthalenes in nearly quantitative yield⁴⁷ (Scheme V). The thermal instability of these benzocyclobutenes has been exploited in the stereospecific synthesis of several

Scheme V



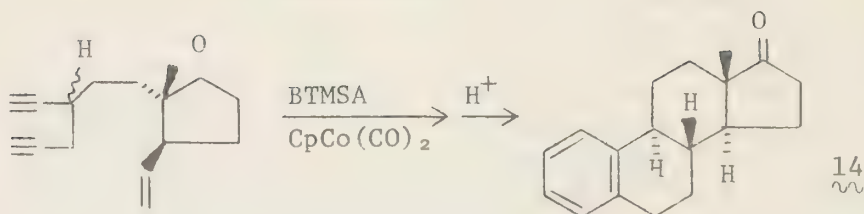
complex polycyclic compounds⁴⁸ (Scheme VI). This type of reaction has been utilized recently, as the final step in an elegant synthesis of the

Scheme VI



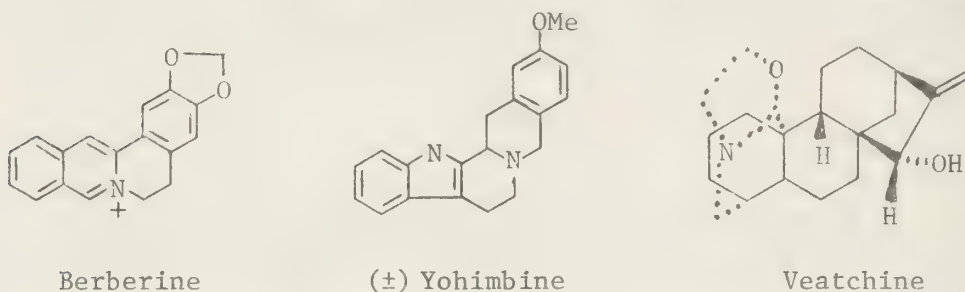
steroid dehydroxyestrone, 14, which was accomplished in overall yield of 28% from alicyclic starting material⁴⁹ (Scheme VII).

Scheme VII



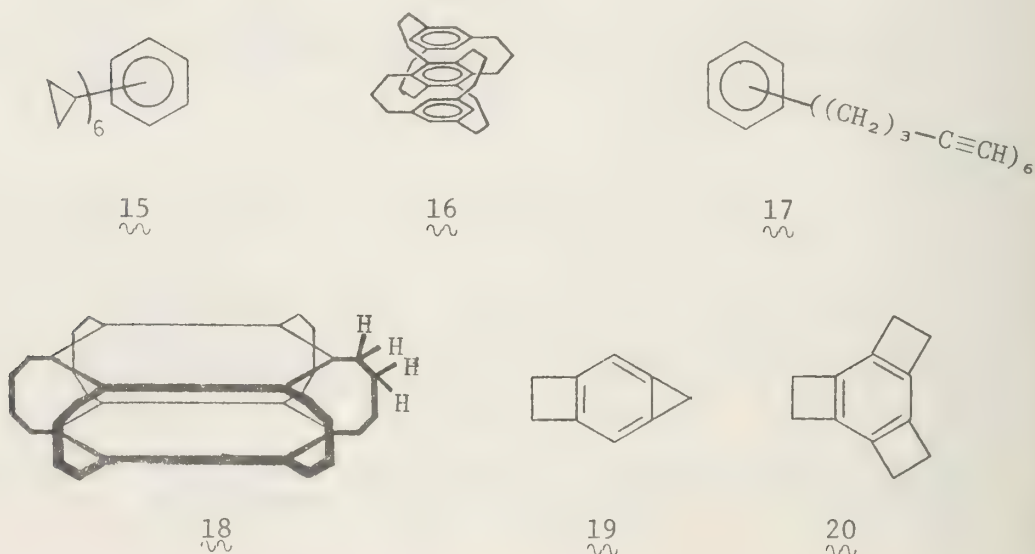
Several investigators⁵⁰⁻⁵³ have utilized benzocyclobutenes as intermediates in complex synthetic schemes, and it is likely that catalytic cooligomerization of substituted 1,5-hexadiynes with functionalized monoacetylenes will be exploited as an efficient entry into this type of synthesis, allowing for extensive control of aromatic substitution. Several natural products or precursors which have been obtained via benzocyclobutenes are given in Figure 4.

Figure 4. Synthetic natural products from benzocyclobutenes



Synthesis of Theoretically Interesting Molecules. The cooligomerization of acetylenes by transition metals presents a method for the synthesis of a variety of theoretically interesting structures (Figure 5). Simple

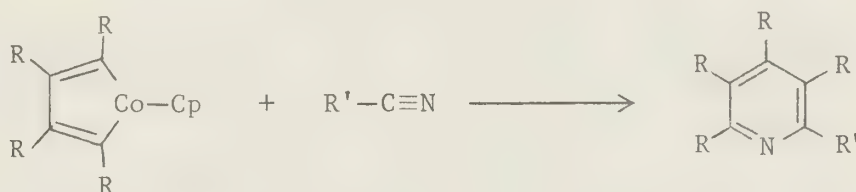
Figure 5. Theoretically interesting molecules via alkyne cooligomerization



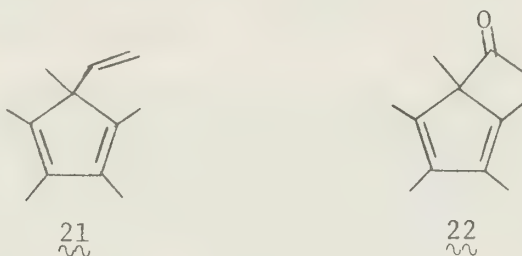
trimerization of dicyclopropylacetylene with $\text{Fe}_3(\text{CO})_{12}$ produced hexacyclopentylbenzene, 15, in 25% yield.⁵⁴ The hexa-bridged tribenzenoid, 16, was formed in 30% yield in the reaction of 17 with Ziegler-type catalysts.⁵⁵ "Percyclophane-4", 18, was isolated in 70% yield by the oligomerization of cyclododeca-1,7-diyne with dimesityl cobalt.⁵⁶ Vollhardt⁵⁷ has reported the synthesis of the strained benzocyclopropane 19 with the crucial step involving catalytic cooligomerization of 1,5-hexadiyne and trimethylsilylpropargyl ether by $\text{CpCo}(\text{CO})_2$. Finally, efforts are underway to isolate the elusive 1,2:3,4:5,6-tricyclobutabenzene, 20, by the internal cyclotrimerization of cyclododeca-1,5,9-triyne.⁵⁸

Miscellaneous Synthetic Targets. Utilization of nitriles as psuedo-alkynes has led to the synthesis of pyridines in good yield by stoichiometric reaction with cyclopentadienyl cobalt complexes⁵⁹⁻⁶¹ (Scheme VIII). Such a reaction has been extended to the synthesis of dipyridines,⁶² and the extension of this reaction to more complex heterocyclic syntheses is in progress.²⁷

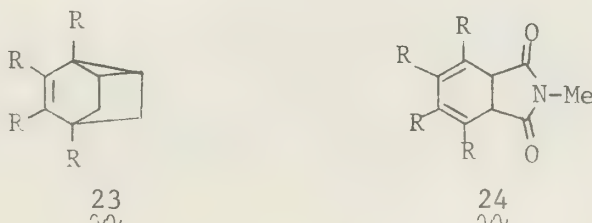
Scheme VIII



The reaction of 2-butyne with a palladium II chloride complex catalyst, followed by treatment with Ph_3Sb or EtOH gave 92-95% yield of 3-vinyl-1,2,3,4,5-pentamethylcyclopentadiene, 21, or 3-acetyl-1,2,3,4,5-pentamethylcyclopentadiene, 22, respectively, and has potential for use in large-scale synthetic applications.⁶³



Heimbach has cooligomerized acetylenes with olefins in the presence of nickel catalysts to give substituted cyclododecatrienes.³¹ Vinyl cyclohexadienes have also been synthesized by this method, and converted via a thermal intramolecular cycloaddition to tricyclo[2.2.2.0^{2,6}]oct-7-enes, 23. Finally, substituted dihydrophthalimides, 24, have been synthesized by reaction of acetylene-metal complexes in the presence of N-methylmaleimide.⁶⁵



BIBLIOGRAPHY

1. K. P. C. Vollhardt, *Acc. Chem. Res.*, 10, 1 (1977).
2. W. Reppe, O. Schlichting, K. Klager, and T. Toupel, *Justus Liebigs Ann. Chem.*, 560 (1948).
3. M. Berthelot and C. R. Hebd, *Seanes Acad. Sci.*, 62, 905 (1866); J. H. Nieuwland and R. R. Vogt, "The Chemistry of Acetylene", Reinhold, New York, N.Y., 1945.
4. C. W. Bird, "Transition Metal Intermediates in Organic Synthesis", Chapt. 1, Logos Press, London, 1967.
5. W. Hübel and C. Hoogzand, in "Organic Synthesis via Metal Carbonyls", Vol. I, I. Wender and P. Pino, eds., Wiley and Sons, New York, N.Y., 1968, p. 343.
6. M. Tanaka and Y. Yamamoto, *Jap. Pat.*, 3819 (1953); *Chem. Abs.*, 48, 8821 (1954).
7. E. F. Lutz, *J. Am. Chem. Soc.*, 83, 2551 (1961).
8. W. Hübel and C. Hoogzand, *Chem. Ber.*, 93, 103 (1960).
9. L. S. Meriwether, E. C. Colthup, G. W. Kennerly, and R. N. Reusch, *J. Org. Chem.*, 27, 3930 (1961).
10. (a) P. Chini, G. DeVenuto, T. Salvatori, and M. DeMolde, *Chemica Industria*, 46, 1049 (1964); (b) B. Franzus, P. J. Canterino, and R. A. Wickliffe, *J. Am. Chem. Soc.*, 81, 1514 (1959); (c) A. D. Furlani, E. Cervone, and M. A. Biancifiori, *Rec. Trav. Chim.*, 81, 585 (1962); (d) K. Higashiura, S. Yokomichi, and M. J. Oiwa, *J. Chem. Soc. Jap., Ind. Chem. Sect.*, 66, 379 (1963).
11. (a) C. H. McKeever and J. O. Von Hook, *U. S. Pat.* 2,542,551; *Chem. Abs.*, 45, 7591 (1951); (b) J. O. Von Hook and W. J. Croxall, *U. S. Pat.* 2,613,208; *Chem. Abs.*, 48, 2772 (1954).
12. W. Hübel and U. Krüerke, *Chem. Ber.*, 94, 2829 (1961).
13. W. Hübel and R. Meréyi, *Chem. Ber.*, 96, 930 (1963).
14. S. N. A. M. S. p. A., *Fr. Pat.* 1,397,654; *Chem. Abs.*, 63, 8285 (1965).
15. J. O. Rose and F. S. Statham, *J. Chem. Soc.*, 69 (1950).
16. L. Malatesta, G. Santarella, L. M. Varrino, and F. Zingales, *Angew. Chem.*, 72, 34 (1960).
17. A. T. Blomquist and P. Maitlis, *J. Am. Chem. Soc.*, 84, 2329 (1962).
18. D. Pollock and P. M. Maitlis, *Can. J. Chem.*, 44, 2673 (1966).
19. G. M. Whitesides and W. J. Ehmann, *J. Am. Chem. Soc.*, 91, 3800 (1969).
20. K. P. C. Vollhardt and R. G. Bergman, *J. Am. Chem. Soc.*, 96, 4996 (1974).
21. E. Müller and C. Beissner, *Chem.-Ztg.*, 96, 170 (1972).
22. E. Müller and A. Segnitz, *Chem. Ber.*, 106, 35 (1973).
23. J. J. Eisch and J. E. Galle, *J. Organometal. Chem.*, 96, C23-C26 (1975).
24. H. Suzuki, K. Itoh, Y. Ishii, K. Simon, and J. A. Ibers, *J. Am. Chem. Soc.*, 98, 8494 (1976).
25. W. H. Baddley and G. B. Tupper, *J. Organometal. Chem.*, 67, C16-18 (1974).
26. H. H. Brintzinger and W. S. Lee, *J. Organometal. Chem.*, 127, 93 (1977).
27. K. P. C. Vollhardt, personal communication.
28. P. M. Maitlis, P. M. Bailey, and B. E. Mann, *J. Chem. Soc. Chem. Commun.* 238 (1976).
29. E. Müller, *Synthesis*, 762 (1974).
30. K. P. C. Vollhardt and R. L. Funk, *J. Am. Chem. Soc.*, 98, 6755 (1976).
31. P. Heimbach and K. J. Ploner, *J. Liebigs. Ann. Chem.*, 54 (1976).
32. R. L. Hillard, III, and K. P. C. Vollhardt, *Angew. Chem.*, 87, 744 (1975); *Angew. Chem., Int. Ed. Engl.*, 14, 712 (1975).
33. R. Hillard, III, and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 99 4058 (1977).

34. E. Müller, W. Winter, and H. Muhm, J. Liebigs Ann. Chem., 754, 77 (1971).
35. E. Müller and W. Dilger, Chem.-Ztg., 97, 388 (1973).
36. E. Müller and G. Odenigbo, Chem.-Ztg., 97, 387 (1973).
37. E. Müller, A. Scheller, W. Winter, F. Wagner, and H. Meier, Chem.-Ztg., 99, 155 (1975).
38. E. Müller and W. Winter, Chem. Ber., 105, 2523 (1972).
39. E. Müller and W. Winter, J. Liebigs Ann. Chem., 761, 14 (1972).
40. E. Müller and G. Zountsas, J. Liebigs Ann. Chem., 758, 16 (1972).
41. E. Müller and G. Zountsas, Chem. Ber., 105, 2529 (1972).
42. E. Müller, R. Thomas, M. Sanerbien, E. Langer, and D. Streichfuss, Tetrahedron Lett., 521 (1971).
43. A. S. Kende, Y.-G. Tsay, and J. E. Mills, J. Am. Chem. Soc., 98, 1968 (1976).
44. F. Arcamone, G. Franceschi, P. Orezzi, G. Cossinelli, W. Barbieri, and R. Mondelli, J. Am. Chem. Soc., 86, 5334 (1964).
45. F. Arcamone, G. Franceschi, and S. Penco, Tetrahedron Lett., 1007 (1969).
46. M. Wani, H. L. Taylor, M. E. Wall, and A. T. McPhail, J. Am. Chem. Soc., 97, 5955 (1975).
47. K. P. C. Vollhardt and R. L. Funk, J. Chem. Soc. Chem. Commun., 834 (1976).
48. K. P. C. Vollhardt and R. L. Funk, J. Am. Chem. Soc., 98, 5755 (1976).
49. K. P. C. Vollhardt and R. L. Funk, J. Am. Chem. Soc., 99, 5483 (1977).
50. T. Kametani, M. Kajiwara, and K. Fukumato, Tetrahedron, 30, 1043, 1053 (1973).
51. W. Oppolzer, J. Am. Chem. Soc., 93, 3833 (1971).
52. P. G. Sommes, Tetrahedron, 32, 405 (1976).
53. (a) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, and K. Fukumato, J. Am. Chem. Soc., 98, 3378 (1976); (b) T. Kametani, Y. Kato, T. Hondo, and K. Fukumato, Heterocycles, 4, 241 (1976).
54. V. Usieli, R. Victor, and S. Sorel, Tetrahedron Lett., 2705 (1976).
55. A. J. Hubert, J. Chem. Soc. (C), 6,11,13,1984 (1967).
56. R. D. Stephens, J. Org. Chem., 38, 2260 (1973).
57. K. P. C. Vollhardt and C. J. Seward, Tetrahedron Lett., 4539 (1975).
58. K. P. C. Vollhardt and A. J. Barkovich, J. Am. Chem. Soc., 98, 2667 (1976).
59. Y. Wakatsuki and H. Yamazaki, J. Chem. Soc. Chem. Commun., 280 (1973).
60. Y. Wakatsuki and H. Yamazaki, Tetrahedron Lett., 3383 (1973).
61. H. Bönemann, R. Brinkmann, and H. Schenkhuhn, Synthesis, 575 (1974).
62. H. Bönemann and R. Brinkmann, Synthesis, 600 (1975).
63. P. M. Maitlis, H. Reinheimer, and J. Moffat, J. Am. Chem. Soc., 92, 2285 (1970).
64. P. Heimbach, K. J. Ploner, and F. Thömel, Angew. Chem. Int. Ed. Eng., 10, 276 (1971).
65. A. J. Chalk, J. Am. Chem. Soc., 94, 5928 (1972).

ORGANIC SYNTHESIS ASSISTED BY HYDROGEN BONDING

Reported by Keith Drengler

October 31, 1977

Potassium fluoride has been a very useful reagent in organic synthesis.¹ It is best known for its fluorinating ability in halogen exchange reactions.² It has also been reported to serve as a base in condensation reactions.³ The major drawback in using potassium fluoride is that a protic solvent is needed to effectively dissolve both the ionic salt and the organic reactant. Such solvents tend to solvate the anion through strong hydrogen bonding and thus reduce, sometimes significantly, the anion's reactivity. However, if this problem is viewed with the idea that the formation of a hydrogen bond can result in the directing of electron density back to the organic molecule involved, then hopefully the organic molecule will be more reactive, resulting in a potentially useful synthetic process. It is the development of such a process which is the topic of this seminar.

Emsley has found potassium fluoride to be very soluble in glacial acetic acid.^{4,5} This is due to the formation of a very strong hydrogen bond between the fluoride anion and the solvent.⁵⁻⁷ It was originally hoped that this system might facilitate homogeneous fluorinations in halogen exchange reactions. It was found that only very activated C-Cl bonds (i.e. acid chlorides) were exchanged.⁸ In the same study, Clark and Emsley showed that when several ω -chlorocarboxylic acids ($\text{Cl}(\text{CH}_2)_n\text{CO}_2\text{H}$; $n=1-4$) were mixed with potassium fluoride in glacial acetic acid, acetoxylation and lactone formation occurred without fluorination.⁸ Apparently, what happens is that the fluoride anion forms a very strong hydrogen bond to the hydroxyl hydrogen. This reduces the nucleophilicity of the fluoride anion while increasing the nucleophilicity of the carboxylate oxygen. Acetoxylation occurs when the hydrogen bond is formed with the solvent (acetic acid), leading to substitution on the reactant (ω -chlorocarboxylic acid). Lactonization proceeds when the hydrogen bond is formed with the reactant leading to intramolecular substitutions.

The concept of hydrogen-bond-assisted reactions has also been expanded further by Clark and Miller. Aromatic⁹⁻¹¹ and cyclic aliphatic⁹ compounds possessing hydrogen bond donors (i.e. -O-H, -S-H, -N-H) react cleanly with halogenoalkanes in the presence of potassium fluoride to give high yields of coupled products. The formation of a methylenedioxy group from a 1,2-dihydroxy aromatic compound¹¹ by this method is of interest since this group occurs frequently in natural products¹² and can also be used as a protecting group.¹³

Phenacyl esters are useful in organic chemistry as derivatives of carboxylic acids¹⁴ and protecting groups.¹⁵ Traditional methods of preparation suffer many drawbacks.¹⁴ Clark and Miller¹⁶ reported high yield conversions (>90%) at room temperature in less than ten minutes by treating α -bromoacetophenone with the carboxylic acid in the presence of potassium fluoride.

Alkylation of β -dicarbonyl compounds is difficult due to concurrent C- and O-alkylation.¹⁷ Attempts to increase the yields of mono-C-alkylated products have been based on shielding the oxygen atom.¹⁸ Clark and Miller¹⁹ report rapid and efficient mono-C-alkylation using tetra-alkylammonium fluoride in yields exceeding 90%. The fluoride ion hydrogen bonds to the hydroxyl hydrogen of the enol tautomer. This renders the molecule nucleophilic and shields the oxygen to inhibit O-alkylation. Such a hydrogen

bonded complex can also be used to render tetra-alkylammonium fluorides anhydrous.¹⁹ If potassium fluoride is used in place of tetra-alkylammonium fluoride, then the β -dicarbonyl compounds will self-condense.^{20,22}

Hydrogen bonding is capable of playing a significant and deliberate role in organic synthesis. The scope of such a process seems unlimited since there are not many organic molecules which are totally incapable of forming a hydrogen bond.²¹

BIBLIOGRAPHY

1. M. Hudlicky, "Chemistry of Organic Fluorine Compounds", Macmillan, New York, N.Y., 1962.
2. (a) A. K. Barbour, L. F. Belf, and M. W. Buxton, *Adv. Fluorine Chem.*, 3, 181 (1963); (b) J. T. Maynard, *J. Org. Chem.*, 28, 112 (1963); (c) A. McMahon, University of Illinois Organic Seminar Abstracts, p. 58, 1976-77, and references cited therein.
3. (a) L. Rand, D. Haidukewych, and R. J. Dolinski, *J. Org. Chem.*, 31, 1272 (1966); (b) L. Rand, W. Wanger, and L. R. Kovac, *J. Org. Chem.*, 27, 1034 (1962); (c) L. Rand, J. V. Swisher, and C. J. Cronin, *J. Org. Chem.*, 27, 3505 (1962); (d) L. Rand and M. J. Albinak, *J. Org. Chem.*, 25, 1837 (1960).
4. J. Emsley, *J. Chem. Soc. (A)*, 2511 (1971).
5. J. Emsley, *J. Chem. Soc. (A)*, 2702 (1971).
6. J. H. Clark and J. Emsley, *J. Chem. Soc., Dalton Trans.*, 2154 (1973).
7. J. H. Clark and J. Emsley, *J. Chem. Soc., Dalton Trans.*, 1127 (1974).
8. J. H. Clark and J. Emsley, *J. Chem. Soc., Dalton Trans.*, 2129 (1975).
9. J. H. Clark and J. M. Miller, *J. Am. Chem. Soc.*, 99, 498 (1977).
10. J. H. Clark and J. M. Miller, *J. Chem. Soc. Chem. Commun.*, 229 (1976).
11. J. H. Clark, L. Holland, and J. M. Miller, *Tetrahedron Lett.*, 3361 (1976).
12. F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963.
13. J. F. McOmie, "Protective Groups in Organic Chemistry", Plenum, London, 1973.
14. R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 5th ed., John Wiley and Sons, Inc., New York, N.Y., 1964.
15. J. B. Hendrickson and C. Kandall, *Tetrahedron Lett.*, 343 (1970).
16. J. H. Clark and J. M. Miller, *Tetrahedron Lett.*, 599 (1977).
17. H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Inc., Menlo Park, Calif., 1972.
18. (a) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Am. Chem. Soc.*, 85, 1141 (1963); (b) E. C. Taylor, G. H. Hawks, and A. McKillop, *J. Am. Chem. Soc.*, 90, 2421 (1968).
19. (a) J. H. Clark and J. M. Miller, *J. Chem. Soc. Chem. Commun.*, 64 (1977); (b) J. H. Clark and J. M. Miller, *J. Chem. Soc. Perkin I*, 1743 (1977).
20. J. H. Clark and J. M. Miller, *Tetrahedron Lett.*, 139, 1422 (1977).
21. R. D. Green, "Hydrogen Bonding by C-H Groups", John Wiley and Sons, Inc., New York, N.Y., 1974.
22. J. H. Clark and J. M. Miller, *J. Chem. Soc. Perkin I*, 2063 (1977).

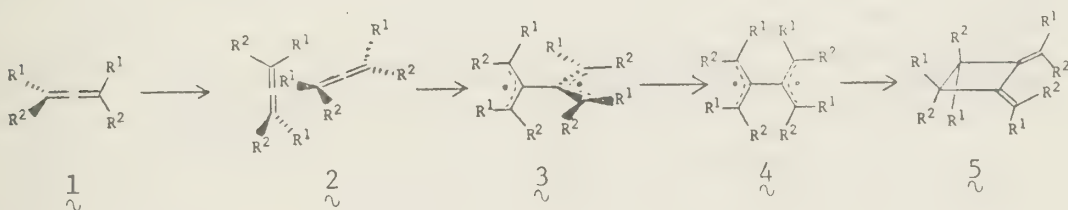
THE MECHANISM OF ALLENE-ALLENE CYCLOADDITION REACTIONS

Reported by William Guilford

November 3, 1977

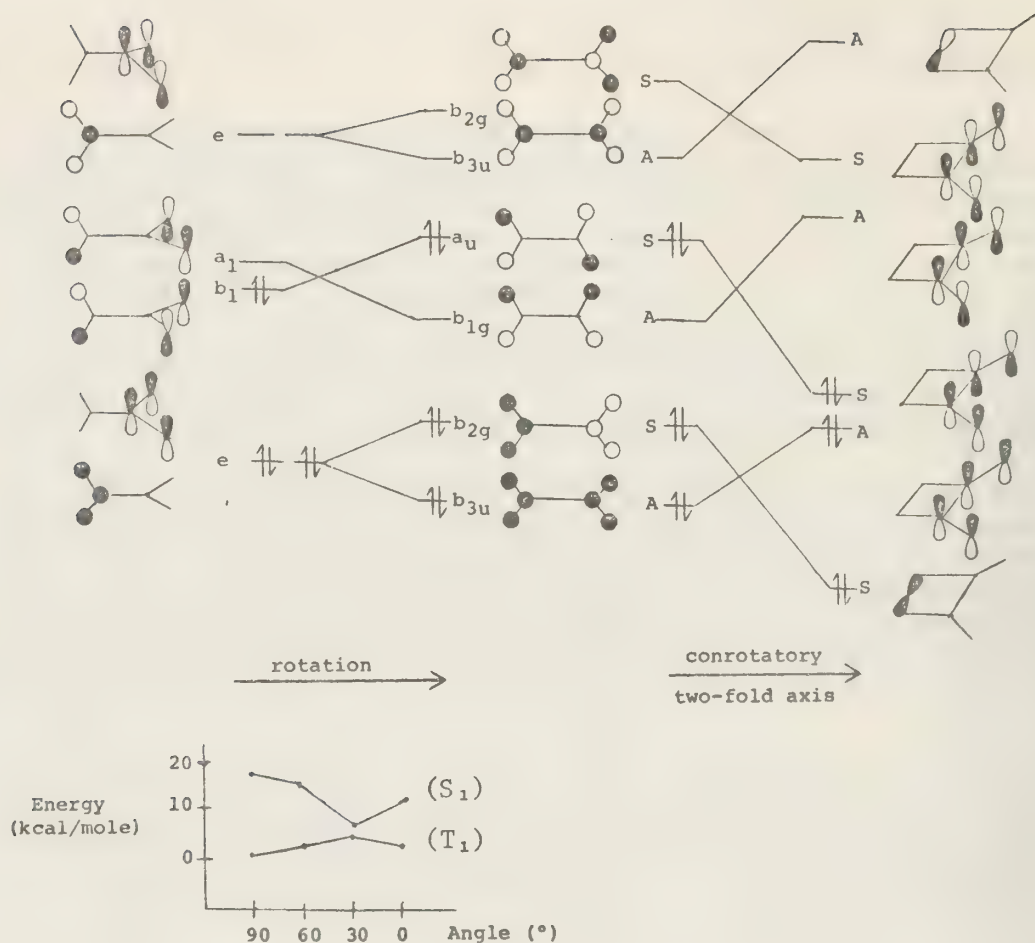
Allenes are the first member of a class of compounds known as the cumulenes and have the following basic structure: $R_2C=C=CR_2$. Even though allenes have been known for over 90 years, it has been within the past two decades that allene chemistry has been explored and developed, generating numerous review articles.¹ Cycloaddition reactions of allenes have enjoyed the same attention in such areas as the photochemical addition to α,β -unsaturated cyclohexenones,² thermal addition to ketenes,³ and the thermal addition to olefins.^{1g,4} This review will concentrate on the mechanistic studies of the cycloaddition reaction between two allenes, which have shown that the dimerization of allenes proceeds through a diradical intermediate.

Numerous examples of substituted allene dimerization reactions have been reported and reviewed.^{1g,1h} In these reactions the following trends were noted: (a) 1,2-dimethylenecyclobutane (5) was formed to the exclusion of 1,3-dimethylenecyclobutane,⁵ (b) trans ring substitution is preferred over cis, and (c) syn geometry about the double bonds is preferred over anti. These trends, as well as other characteristics of the reaction, can be explained through the following mechanism. The two substituted allenes



(1, $R^2 > R^1$) approach each other in an approximate perpendicular fashion (2) forming a bond between their center carbon atoms. Disrotatory rotation of the allyl methylenes to form the planar allyl radicals gives the singlet bisallyl diradical 3 which closes to product 5 by rotating toward the planar diradical 4 and rotation of the methylenes of the allyl groups in a conrotatory manner. The stereochemistry of the products is determined (a) through the formation of bisallyl diradical 3 and (b) through rotation about the central bond to approach 4. In both of these steps, steric interaction plays an important directive role. The preferred configuration of the bisallyl intermediate is shown by 3 with one of the larger R groups facing forward toward the other allene and the other back. This configuration has the least steric strain on the allyl radicals, but the energy difference between this configuration and the both forward and both back configurations can be slight, so products from all three configurations are formed. It should be noted that products arising from the configuration shown in 3 yields trans ring substitution and syn geometry on the double bonds. Once 3 is formed, rotation about the central bond can occur giving a kinetic product from the least sterically hindered transition state. The kinetic product can reopen in a conrotatory fashion to give, after rotation through a more sterically hindered transition state and conrotatory ring closure, a more thermodynamically stable product.

The conrotatory ring formation and ring opening can be explained through the use of molecular orbital correlation diagrams⁶ derived from a Pariser-Parr-Pople procedure specifically adapted for examining twisting



motions and non-planar π -electron systems.⁷ Inspection of the π -molecular orbitals for the orthogonal bisallyl diradical **3** shows that they are formed from two independent allyl radicals which only interact through spiroconjugation in orbitals a_1 and b_1 , lowering b_1 and raising a_1 . If the angle between the allyl radicals is reduced from 90° to 0° , the planar singlet diradical **4** is formed in a doubly excited state. Inspection of the symmetry of the orbitals in **4** and **5**, assigned using a two-fold axis of symmetry required for conrotatory motions, shows that the symmetry is right for ring closure. Ring opening to give the bisallyl intermediate will follow the reverse of this path and not a disrotatory ring opening. This can be explained by noting that a disrotatory ring opening would populate the b_{3u} , b_{2g} and b_{1g} orbitals on **4**, but with rotation to the orthogonal diradical **3**, the b_{1g} orbital would be raised in energy to populate the a_1 orbital which would form a doubly excited state in **3**, making disrotatory ring opening to the orthogonal bisallyl intermediate an energetically unfavorable transition.

Calculations have been done on the rotation from the orthogonal to the planar singlet diradical (S_1) using the MINDO/2 method.⁸ These calculations show an energy minimum at an angle of 30° , 8 kcal/mole below the orthogonal state and 4 kcal/mole below the planar state. This result shows that there is a strong driving force for rotation and that the orthogonal state is higher in energy than the planar state.

The biradical mechanism is supported by the studies of Dolder and Dai⁹ on secondary deuterium isotope effects. Nondeuterated and 1,1-

dideuterated allene were heated in a sealed tube with benzene at 140° to 5% conversion into products, 91% of which was cyclobutane products. Analysis of the product mixture through nmr comparison of allyl to vinyl protons gave an intramolecular deuterium isotope effect of 1.14 (average for three runs). The reaction was repeated going to 4.1 to 6.3% conversion with tetradeuterated and non-deuterated allene and by nmr analysis of the product mixture and intermolecular isotope effect of 1.02 (average for three runs) was obtained. Similar studies on Diels-Alder reactions showed no difference between inter- and intramolecular isotope effects. This result is consistent only with a two-step mechanism.

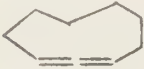
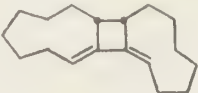

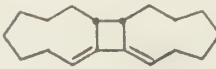
Kinetic studies have been done by Detzer and Roedig¹⁰ on various substituted allenes. These dimerization reactions were shown to follow second order kinetics and had similar activation parameters to Diels-Alder¹¹ and 1,3-dipolar addition reactions,¹² but unlike other cyclo-addition reactions, electronic effects were shown to be more important than steric effects.^{12,13} A qualitative correlation between the electron-withdrawing ability of the substituent and the relative reaction rate (K_I/K_{II}) is apparent. It was also shown that there is a direct correlation between the ¹³C nmr resonance of the central carbon atom of substituted allenes and electron density calculations¹⁴ using the CNDO/2 method of Pople,¹⁵ with electron withdrawing groups lowering the electron density. Considering the rate-determining step to be formation of the

	K_I/K_{II}	ΔH^\ddagger	ΔS^\ddagger
$Cl_2C=C=CClCN$	3.00	---	---
$Cl_2C=C=CClCOOEt$	1.48	8.4 ± 0.8	-45.0 ± 4.5
$Cl_2C=C=CCl_2$	1.00	10.6 ± 3.1	-42.1 ± 11.2
$Cl_2C=C=CClPh$	0.65	14.6 ± 3.6	-36.8 ± 8.6
$Cl_2C=C=CClBr$	0.63	13.8 ± 1.8	-38.8 ± 4.8
$Cl_2C=C=CBr_2$	0.23	15.0 ± 2.2	-34.9 ± 4.8

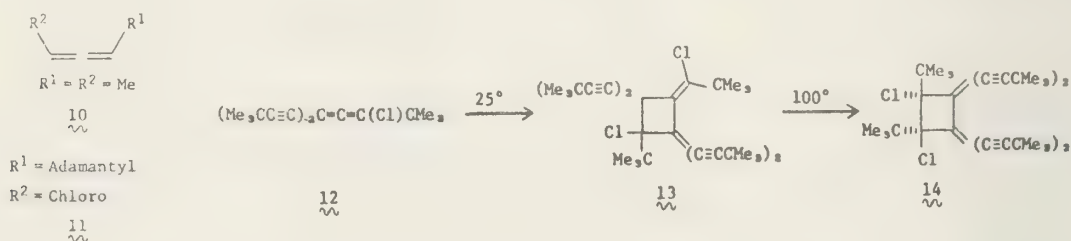
orthogonal bisallyl intermediate and noting that ΔH^\ddagger decreases with increasing electron-withdrawing properties of the substituent; it can be concluded that the decreased electron density on the central carbon atom destabilizes the allene and thereby increases the rate of reaction.

The thermal dimerization of d and dl cyclononadiene (6)¹⁶ demonstrates the stereoselectivity of both steps of the allene dimerization reaction. Diene 8 is the product expected from the less sterically demanding approach of the d and l isomers of allene 6 followed by a disrotatory methylene rotation to the orthogonal bisallyl intermediate which can close via rotation and conrotatory motions. Diene 9 is the product expected from the same less sterically demanding approach of the d and d isomers of allene 6 followed by similar rotatory motions to ring closure. This mechanism predicts two different bisallyl intermediates. In the case of d and l isomers, the intermediate has the ring carbons both back on both allyl groups, but in the case of the d and d isomers, the intermediate has one back and one forward on one allyl group and both back on the other. Further study shows that diene 7 is formed from the confirmation of one back and one forward on both allyl groups, a more sterically strained intermediate, so a disrotatory motion would be preferential in the opposite

direction to give the bisallyl intermediate which gives diene 8. This is the only example where a disrotatory methylene rotation is confirmable, and clearly shows the effect of the formation of the bisallyl diradical intermediate on the stereoselectivity of the reaction.

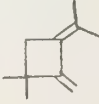
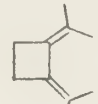


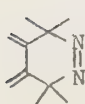

			
6	7	8	9
d1	6.3	62.5	31.5
d (>90%)	0.4	11.9	88.1

The preference for syn geometry about the double bonds and trans ring stereochemistry is shown in the studies by Gajewski and Black¹⁷ using 2,3-pentadiene (10) and by Jacobs and Muscio¹⁸ using 1-adamantyl-3-chloroallene (11). The difference between the ratios and the stereoselectivity can be explained by the occurrence of several bisallyl intermediates of similar steric requirements. The formation of a single bisallyl intermediate of low steric demand explains the single isomer (13) reported by Miller and Migliorese¹⁹ from the thermal dimerization of allene 12 at 25° in hexane. Heating of diene 13 at 100° causes isomerization to diene 14 in quantitative yield. The initial formation of 13 is explained by rotation of the bisallyl intermediate to the less sterically hindered transition state to ring closure. The formation of diene 14 is explained at the higher temperature by ring opening of 13 followed by rotation through



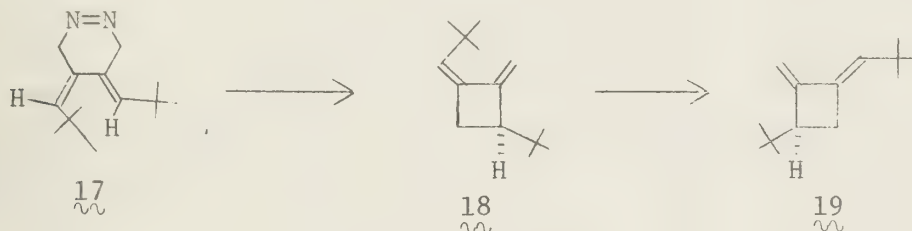
the more sterically hindered transition state to conrotatory ring closure. It should be noted that the geometry about the double bond in 13 is syn and the ring substitution in 14 is trans, the result of the less sterically demanding bisallyl intermediate.

Studies by Levek and Kiefer²⁰ on the thermal reactions of 3-methyl-1,2-butadiene (15) and azo compound 16 clearly indicate the intermediacy

	Temp	Rxn Type			
	151	Δ	35.0	47.5	17.5
	151	Δ	36.0	46.7	17.3
	35	Δ	~ 33	~ 53	~ 14
	34.5	$h\nu$	~ 32	~ 53	~ 15

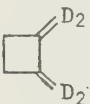
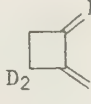
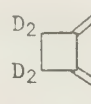
of a bisallyl diradical. The thermal dimerization of 15 and the thermal expulsion of nitrogen from 16 give product distributions which are best explained by postulating a common intermediate as the bisallyl diradical. Further evidence for this intermediate is seen in the product distribution of the thermal and photochemical reactions of 16.

The formation of a thermodynamically unstable product through rotation of a bisallyl intermediate in the less sterically demanding manner is indicated in work by Kellogg and Beetz²¹ on the thermal expulsion of nitrogen from azo 17. Compound 17 can be converted into diene 18 at 190° and












immediate distillation of 18 from the reaction mixture; if 18 is resubmitted to the reaction conditions, it totally isomerizes to the sterically less hindered diene 19.

Studies by Gajewski²² on the thermal and photolytic rearrangement of tetradeuterated diene 20 have indicated a singlet biradical intermediate.

				
	Rxn Time	<u>20</u>	<u>21</u>	<u>22</u>
Thermal	3.25 hr	74.3	17.4	8.3
	12.33 hr	46.6	35.8	17.3
	19.0 hr	40.1	42.5	17.4
Photolytic	8.25 min	92.5	5	2.4
	20 min	69.7	20.5	9.8

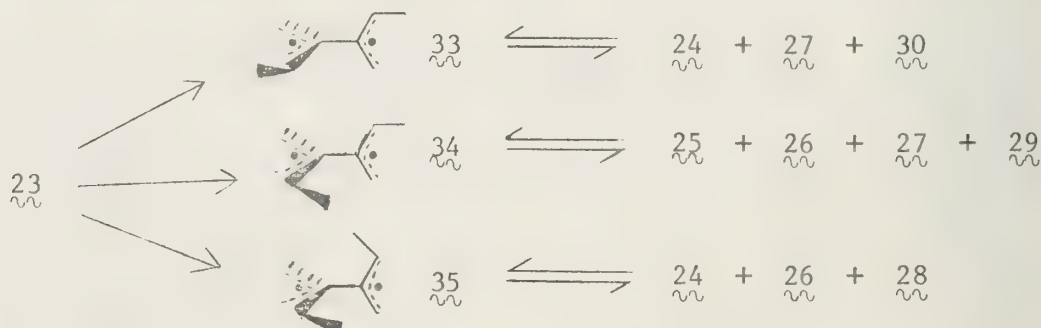
Diene 20 was heated in the gas phase at 278° and photolyzed at 254 nm in cyclohexane. The products were analyzed by nmr through comparison of vinyl to allyl protons and by mass spectrometry after conversion to an aromatic derivative; the results are in good agreement. The results show a 2:1 ratio between 21 and 22, which is statistically consistent with the idea that once the bisallyl intermediate is formed, it can close in two ways to form 21 and in one way to form 20 or 22. Other possible intermediates have been looked at and eliminated on energetic or statistical grounds. Evidence for a radical intermediate comes from the photolysis of diene 20 in deuterated cyclohexane (C₆D₁₂) where H-D exchange was noted in the recovered starting material; these results are similar to the results obtained by Borden.²³ This exchange and the isomerization was not effected by the addition of nitrogen, oxygen or triplet quencher di-*tert*-butyl nitroxide and upon addition of triplet sensitizer acetophenone, only dimeric products were obtained with no observed deuterium scrambling. These results are consistent with a singlet biradical intermediate.

Further studies by Gajewski^{22,24} on the dimerization of 1,2-butadiene (23) and on the gas phase thermal rearrangement of its dimer products 24, 25, 26, 28, and 29 have given results which are consistent only with a

Cmpd	Temp	Time (hr)									
CH ₃ CH=C=CH ₂	170	1	25	4	37	18	13	3	0.5	--	--
23	"	13	10	2	35	14	29	11	2	--	--
	"	20	4	0.6	25	7	46	15	2.5	--	--
24	254.7	0.5	79	0.0	trace	19.3	0.0	0	0.7	0.4	0.0
	"	1	60	0.0	0.4	37.4	0.0	trace	1.7	0.8	trace
	"	1.5	45	0.0	0.3	45.9	0.0	trace	4.4	3.0	1.5
25	"	0.5	trace	81.8	4.2	0.4	0.0	0.9	0.0	11.3	1.4
	"	1.0	trace	70	7.6	1.5	0.0	2.0	0.0	15.2	3.0
	"	1.5	trace	40	8.4	8.4	0.0	4.2	0.0	33.7	5.1
26	"	0.5	0.2	0.4	14.1	4.7	0.0	0.9	0.0	75.3	4.1
	"	1.0	0.0	trace	1.0	2.1	0.0	0.8	0.0	90.0	5.9
28	"	0.5	0.0	0.0	1.0	0.0	36.2	1.9	0.0	1.9	58
	"	1.0	0.0	0.0	0.0	0.0	13.8	3.5	0.0	1.8	80.6
29	"	0.5	0.0	0.0	0.2	0.0	0.6	49.7	0.9	0.3	40.2
	"	1.0	0.0	0.0	0.0	0.0	0.0	23.6	1.6	1.0	73.8

bisallyl intermediate. From the results, the following trends should be noted: diene 24 gives predominately 27 and 30 for diene products; diene 25 gives predominately 26, 27, and 29 as diene products and triene product 31; diene 28 is formed only in the dimerization of 23; dienes 26, 28, and 29 give predominately triene 31, 32, and 32, respectively. These results can be explained through the formation of three bisallyl intermediates 33, 34, and 35 and the rearrangement to the thermodynamically more stable products.

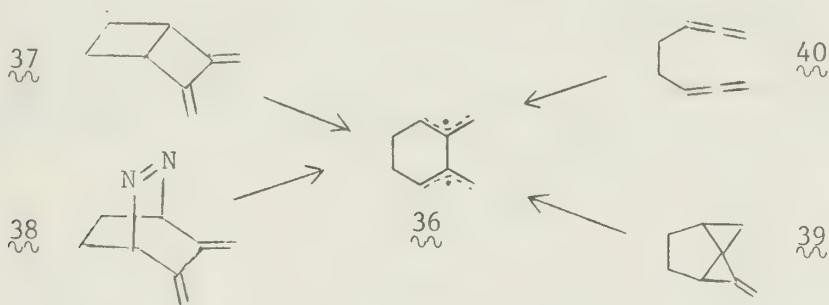
The dimerization of 1,2-butadiene (23) can form three possible bisallyl intermediates 33, 34, and 35 which upon conrotatory ring closure give the products shown. Upon conrotatory ring opening of the diene products, they will return to one of the allowed bisallyl intermediates; it should be noted that several dienes, 24, 27, and 26, can reopen to form two different bisallyl intermediates. The bisallyl intermediate can rotate 180° and, through conrotatory ring closure, form one of the other products



allowed from that intermediate. The formation of predominately one set of compounds from the isomerization of 24 and 25 is explained by this mechanism. Special note should be taken of the ring opening of 24, which can form intermediate 35 but does not show products from that intermediate. This result is explained by steric interaction in the conrotatory ring opening by the two methyl groups making this mode of ring opening unfavorable with respect to ring opening to give 33. The drive to the thermodynamically more stable products is shown by the movement of product composition to one or two products in all the cases looked at. The triene products 31 and 32 can be explained by hydrogen transfer during the bisallyl intermediate or through a concerted process. Their formation requires elevated temperatures; no triene product is observed at 170°, and triene formation is rapid and exclusive at 260°, and appears to involve specific precursors, 26 for 31, and 28 or 29 for 32. Gas phase photolysis of 24 and 25 gave a similar, yet less selective, product mixture, compared to the thermal case, but by using triplet quenchers and sensitizers, as noted in the deuterium substituted case (20), it was determined that the reaction proceeded through a singlet diradical.

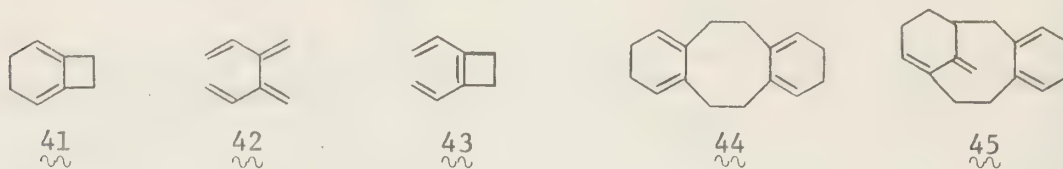
Attempts have been made using esr spectroscopy to observe the triplet diradical, which has been predicted by calculations to be the ground state,⁸ and a triplet diradical has been observed by Dowd.²⁵ The triplet diradical was generated by photochemical expulsion of carbon monoxide at -196° and has an observed half-life of 20 minutes. Similar studies¹⁰ on the dimerization of Cl₂C=C=CClX (X=H, Br, Ph, COOEt, CN) over a wide range of concentrations in CCl₄ and varying conditions failed to observe diradical triplet signals. These results are in agreement with an initially formed singlet bisallyl diradical which quickly closes to products before intersystem crossing can occur.

Positive confirmation of the spin state, spin state products as well as results consistent with the bisallyl intermediate has been accomplished by Roth and Erker.²⁶ The bisallyl intermediate (36) was approached from four different compounds 37, 38, 39, and 40 by thermal and photochemical rearrangements.



The gas phase thermal rearrangement of 37 or 38 at 110° gave an identical product distribution of 41 and 42 (67:33) which was independent of temperature and pressure. Diene 37 was determined not to be an intermediate in the decomposition of 38 by product analysis of the decomposition of 38 in a stationary or gas flow system. The thermal rearrangement of 39 in the gas phase at 310° yields 41, 42, and 43 in ratios which depend on pressure. At low pressure (10⁻² torr), 42 is formed almost exclusively and at high pressure, comparable to a solution reaction, the product ratio of 41 to 42 is 60:40. In the intermediate pressure range, 43 is formed giving a product distribution at one torr of 41, 42, and 43 in a ratio

of 25:60:15. The gas phase thermal rearrangement at 180° of 40 gave products 41 and 42 whose ratio was shown to vary with pressure in the same fashion as with 39. When 43 was heated to 170° in the gas phase, it



rearranged to 41 and 42 which, upon heating to 250°, gave exclusively the thermodynamically more stable product 42. The formation of 41 from these four different compounds can best be explained through a common intermediate 36, and 42 and 43 from isomerization of 41. The pressure dependence of the formation of 41, 42, and 43 can be explained through consideration of the lifetime of the vibrationally hot intermediate 36. If ring closure occurs before 36 can lose its excess energy to collisions, then vibrationally hot 41 will result which can further isomerize. It should be noted that at higher pressures, the product compositions are nearly identical for all four starting compounds.

Solution phase thermal rearrangements of 37, 38, 39, and 40 have been carried out and yield dimers 44 and 45. In each case, CIDNP signals in the nmr were noted for intense emission which corresponded to the absorption signals of dimers 44 and 45; no CIDNP signals were observed in the nmr which corresponded to the absorption signals of 41 and 42 when they were formed in solution. The difference between reactions is attributed to the difference in spin states, the triplet spin state yielding dimer products and the singlet spin state yielding monomer products. The difference between the rate of formation of the triplet state in the gas phase and solution is due to the probability of intersystem crossing.

In conclusion, the dimerization of allenes proceeds through a bisallyl intermediate, an intermediate which has been postulated for other reactions.^{27,28,29} The stereoselective formation and collapse of this bisallyl intermediate can be explained through the use of orbital symmetry. This result is not unexpected and was foreseen by Woodward and Hoffman³⁰ in a concluding remark: "Nor can it be doubted that extension will be made - both of a fundamental and of a detailed nature. Since every elementary step in any chemical reaction is a concerted process, correlative ideas must be applied to all reactions..."

BIBLIOGRAPHY

- (a) H. Fisher, "The Chemistry of Alkenes", ed. by S. Patai, Interscience Publishers, New York, N.Y., 1964, p. 1025; (b) A. A. Petrov and A. V. Fedorova, *Usp. Khim.*, 33, 3 (1964); (c) K. Griesbaum, *Angew. Chem. Int. Ed. Engl.*, 5, 933 (1966); (d) D. R. Taylor, *Chem. Rev.*, 67, 317 (1967); (e) T. F. Rutledge, "Acetylenes and Allenes", Reinhold Book Corp., New York, N.Y., 1969; (f) S. R. Sandler and W. Karo, "Organic Functional Group Preparation", Vol. II, Academic Press, New York, N.Y., 1971, p. 1; (g) J. E. Baldwin and R. H. Fleming, *Fortschr. Chem. Forsch.*, 15, 281 (1970); (h) T. Okamoto, *Bull. Inst. Chem. Res., Kyoto Univ.*, 50, 450 (1972).
- (a) K. Wiesner, *Tetrahedron*, 31, 1655 (1975); (b) F. E. Ziegler and J. A. Klock, *Tetrahedron Lett.*, 315 (1974).

3. (a) W. Weyler, Jr., L. R. Byrd, M. C. Caserio, and H. W. Moore, J. Am. Chem. Soc., 94, 1027 (1972); (b) W. T. Brady, J. D. Stockton, and A. D. Patel, J. Org. Chem., 39, 237 (1974); (c) W. G. Duncan, W. Weyler, Jr., and H. W. Moore, Tetrahedron Lett., 4391 (1973); (d) H. A. Bampfield and P. R. Brook, J. Chem. Soc. Chem. Commun, 171 (1974); (e) H. A. Bampfield, P. R. Brook, and K. Hunt, ibid., 146 (1976).
4. (a) D. R. Taylor, M. R. Warburton, and D. B. Wright, J. Chem. Soc. (C), 386 (1971); (b) D. R. Taylor and D. B. Wright, ibid., 391 (1972); (c) D. R. Taylor, M. R. Warburton, and D. B. Wright, J. Chem. Soc. Perkin I, 1365 (1972).
5. Ya M. Slobodin and A. P. Khitron, Zh. Obshch. Khim., 33, 2822 (1963) and references within.
6. B. G. Odell, R. Hoffmann, and A. Imamura, J. Chem. Soc. (B), 1675 (1970).
7. (a) R. Hoffmann, A. Imamura, and G. D. Zeiss, J. Am. Chem. Soc., 89, 5125 (1967); (b) A. Imamura and R. Hoffman, ibid., 90, 5379 (1968).
8. (a) W. W. Schoeller, Tetrahedron Lett., 2043 (1973); (b) W. W. Schoeller, ibid., 2047 (1973).
9. S. Dai and W. R. Dolbier, Jr., J. Am. Chem. Soc., 94, 3946 (1972).
10. W. Detzer and A. Roedig, Tetrahedron, 27, 5697 (1971).
11. (a) A. Wassermann, Trans. Faraday Soc., 34, 128 (1938); (b) A. Wassermann, ibid., 35, 841 (1939).
12. R. Huisgen, Angew. Chem., 75, 742 (1963).
13. J. Sayer, D. Lang, and A. Mielerk, Angew. Chem., 74, 352 (1962).
14. (a) J. K. Crandall and S. A. Sojka, J. Am. Chem. Soc., 94, 5084 (1972); (b) R. Steur, J. P. C. M. van Dongen, M. J. A. de Bie, W. Drenth, J. W. de Hann, and L. J. M. van de Ven, Tetrahedron Lett., 3307 (1971); (c) W. Runge and J. Firl, Ber. Bunsenges. Phys. Chem., 79, 913 (1975).
15. J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y.
16. W. R. Moore, R. D. Bach, and T. M. Ozretich, J. Am. Chem. Soc., 91, 5918 (1969).
17. J. J. Gajewski and W. A. Black, Tetrahedron Lett., 899 (1970).
18. T. L. Jacobs and O. J. Muscio, Jr., Tetrahedron Lett., 4829 (1970).
19. K. G. Migliorese and S. J. Miller, Tetrahedron, 30, 385 (1974).
20. T. J. Levek and E. F. Kiefer, J. Am. Chem. Soc., 98, 1875 (1976).
21. T. Beetz and R. M. Kellogg, J. Am. Chem. Soc., 95, 7925 (1973).
22. (a) P. A. Kelso, A. Yeshuran, C. N. Shih, and J. J. Gajewski, J. Am. Chem. Soc., 97, 1513 (1975); (b) J. J. Gajewski and C. N. Shih, J. Am. Chem. Soc., 94, 1675 (1972).
23. W. T. Borden, L. Sharpe and I. L. Reich, Chem. Commun., 461 (1970).
24. J. J. Gajewski and C. N. Shih, J. Am. Chem. Soc., 91, 5900 (1969).
25. P. Dowd, J. Am. Chem. Soc., 92, 1066 (1970).
26. (a) W. R. Roth and G. Erker, Angew. Chem. Int. Ed. Engl., 12, 503 (1973); (b) W. R. Roth, M. Heiber, and G. Erker, Angew. Chem. Int. Ed. Engl., 12, 504 (1973); (c) W. R. Roth and G. Erker, ibid., 12, 505 (1973).
27. S. Braverman and D. Seger, J. Am. Chem. Soc., 96, 1245 (1974).
28. P. J. Garratt and S. B. Neoh, J. Am. Chem. Soc., 97, 3255 (1975).
29. P. Vogel and M. Hardy, Helv. Chim. Acta, 57, 196 (1974).
30. R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie GmbH., Academic Press, Inc., Weinheim/Bergstr., 1971, p. 178.

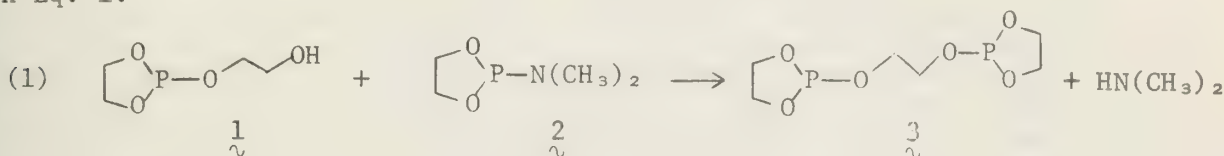
THE SYNTHESIS AND REACTIONS OF PHOSPHORANES WITH A PROTON LIGAND

Reported by Michael R. Ross

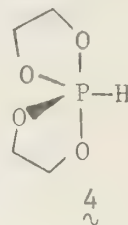
November 7, 1977

This seminar will deal with the preparation, structure, and reactions of P-H phosphoranes, hypervalent P(V) compounds with an equatorial proton ligand that undergo a novel ring-chain P(III)-P(V) tautomeric equilibrium. Most common are those with spiro structures.

The first spirophosphoranes reported in the literature were originally assigned a P(III) structure by Anshutz in 1928,^{1a} and by Burgada^{1b} and Nesterov^{1c} in 1965, based upon the chemical reactivities observed for the compounds; for example, the alcoholysis or aminolysis of a P-N bond is a reaction characteristic of a free -OH or -NH₂ functionality,^{1c} as shown in Eq. 1.

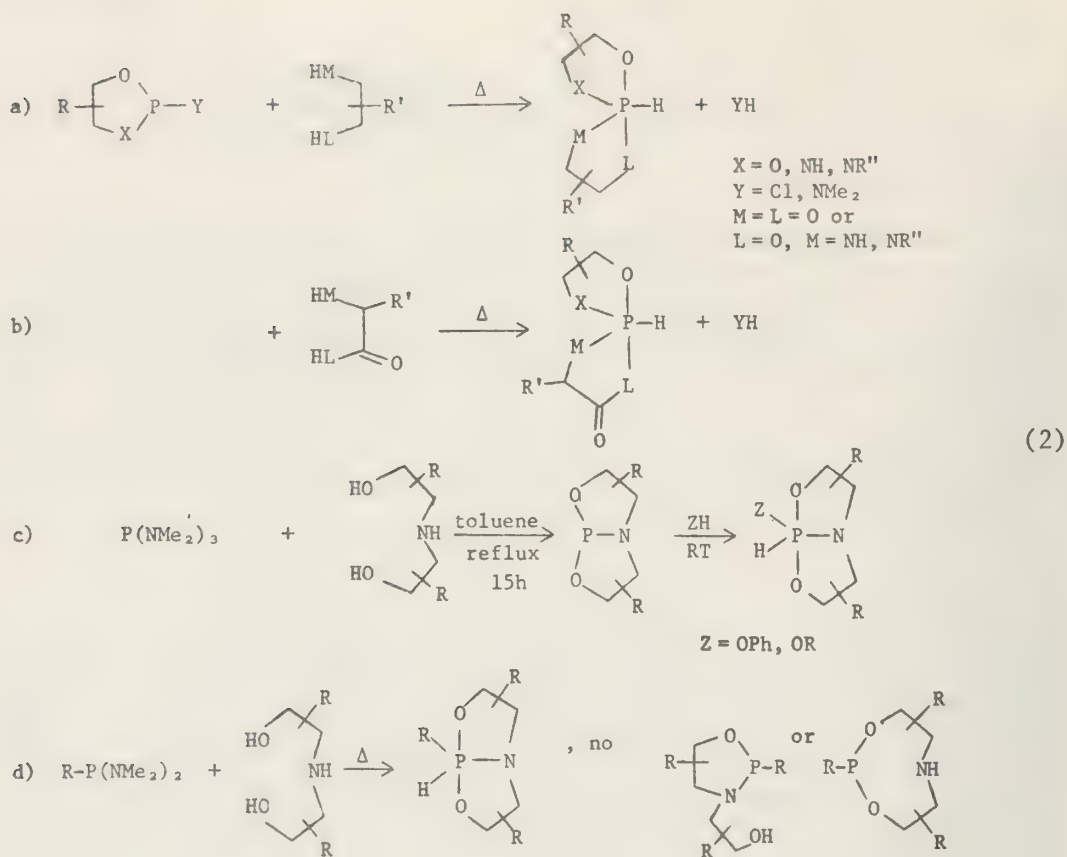


Shortly thereafter, Burgada observed a ¹H nmr for 4, derived from ethylene glycol and PCl₃, with a P-H coupling constant of 830 Hz, compatible with a direct bonding of a proton to phosphorus and thus a P(V) structure,² and in 1967 ³¹P nmr provided further favorable evidence.³ The pentacoordinated spirophosphoranes exhibit phosphorus chemical shifts on the order of δ +35 to +70 (upfield from a H₃PO₄ standard), while the P(III) tautomers show chemical shifts in the -120 to -150 region (downfield from a H₃PO₄ standard), characteristic of phosphite derivatives. Both tautomers are seen in a given ³¹P nmr spectrum, in proportions that vary as a function of temperature, the P(III) tautomer percentage increasing as the temperature is raised.³ This suggests that a P(III)-P(V) equilibrium is operative between the two tautomers.



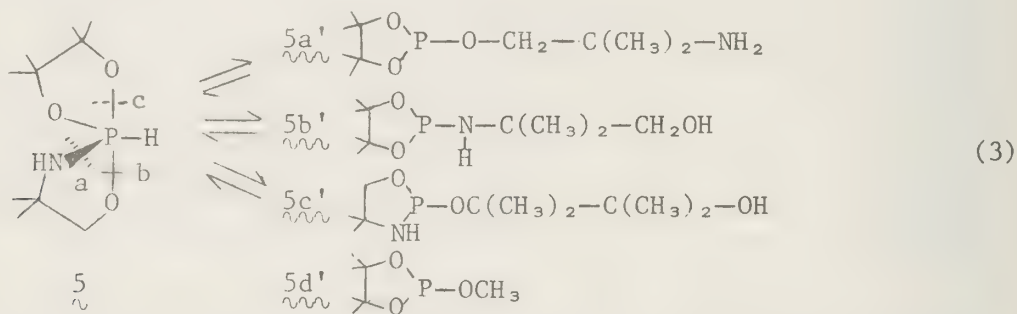
P-H phosphoranes have a nearly perfect trigonal bipyramidal (TBP) geometry, with equatorial angles close to 120° and an apical-apical bond angle of 180°, while other spirophosphoranes without a proton ligand have shown structures varying between square pyramidal and distorted TBP.⁴ Although crystal structure determinations of P-H phosphoranes to date have not succeeded in locating the proton ligand, it is expected from electronegativity arguments,⁵ in which more electronegative ligands prefer to occupy apical positions in the TBP, that the proton would occupy an equatorial position. Another factor favoring an equatorial proton location is that an apical proton would require that one of the rings be fused diequatorial, which has been observed to be unfavorable in cyclic phosphoranes.⁵ Also, the steric compactness of the proton may account for the observed idealized TBP structure for P-H phosphoranes.⁵

P-H phosphoranes have been synthesized from tricoordinate phosphorus compounds (like PCl₃ or aminodioxaphospholanes) and vicinal diols, α-amino alcohols, α-amino acids, and α-hydroxy acids⁶ under mild conditions, as shown in Eq. 2. Eq. 2c is worthy of note as the only example of intermolecular bond insertion known in the literature involving an oxygen-hydrogen bond.



Chemical Properties. Infrared and nmr studies have provided strong evidence in favor of an equilibrium between P(III) and P(V) tautomers⁷ at a variety of temperatures; this has been shown to be a general phenomenon for P-H spirophosphoranes.⁸

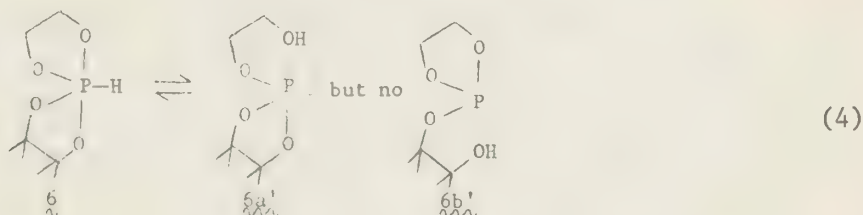
Spirophosphorane 5 has an equilibrium concentration of its P(III) tautomer of 18% at 100°C.⁸ The P(III) structure has been identified as 5a' by ³¹P and ¹H nmr, ruling out possibilities 5b' or 5c', which can be envisioned as resulting from the breaking of bonds a, b, or c in the spirophosphorane, as shown in Eq. 3.⁹ The ³¹P nmr at 100°C showed a doublet



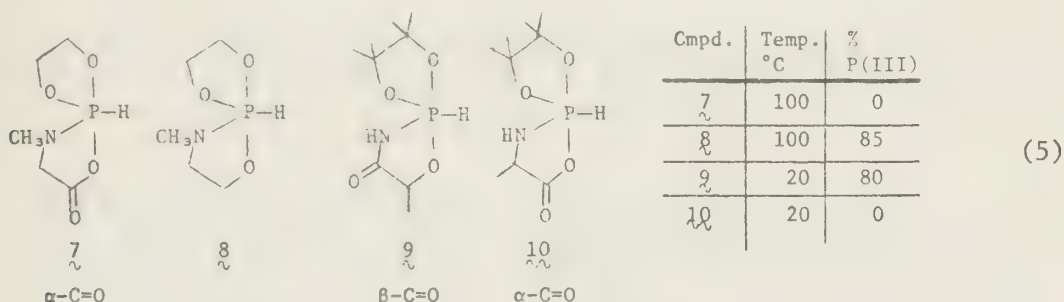
for the phosphorane ($\delta^{31}\text{P} = +53.6$ ppm, $^1J_{\text{PH}} = 774$ Hz) and a weak resonance at -150.4 ppm, a 1-2-1 triplet with a $^3J_{\text{PH}}$ of 10 Hz. The ¹H nmr revealed a doublet at $\delta 3.50$, with a $^3J_{\text{PH}}$ of 10 Hz, consistent only with structure 5a'. A further confirmation may be found through the ³¹P and ¹H nmr spectra of model compound methoxydioxaphospholane 5d', with a quartet at -147 ppm and a $^3J_{\text{PH}}$ of 9.8 Hz in the ³¹P nmr, and a methoxy doublet at $\delta 3.3$, with a J_{PH} of 9.8 Hz, in the ¹H nmr.⁹ Three methyl resonances are also

observed in the ^1H nmr for the P(III) tautomer, at $\delta 1.00$ (equivalent CH_3 , α to N), 1.17 and 1.28 (exo and endo methyls on the phospholane ring), consistent with $5a'$ and $5b'$, but not $5c'$. The diastereotopic methylene ring protons in phospholane $5c'$ form an ABX system, and one might expect a doublet of doublets near $\delta 3.5$ in the ^1H nmr for $5c'$.

There are several major factors that determine the equilibrium position favoring one of the two tautomers and the structure of the P(III) tautomer.⁸ The equilibrium displacement, as measured by ^{31}P nmr, is affected by steric factors determined by the number and nature of substituents on the carbon atoms in the spiro rings and the nature of the N substituent in the mixed azaoxaspirophosphoranes. In all observed aza-oxaspirophosphoranes, bond breaking in the P(V) tautomer always occurs between phosphorus and nitrogen, producing a P(III) tautomer with a free amine group, as in Eq. 3, $5a'$ is seen but $5b'$ is not. Nitrogen substitution by an alkyl group has been observed to favor the P(III) tautomer. An increase in ring substitution decreases the percentage of the P(III) tautomer at equilibrium, with the least substituted ring breaking exclusively, as in Eq. 4, which might be a manifestation of a gem-dialkyl or Thorpe-Ingold effect.¹⁰ It has also been observed that the presence of a carbonyl

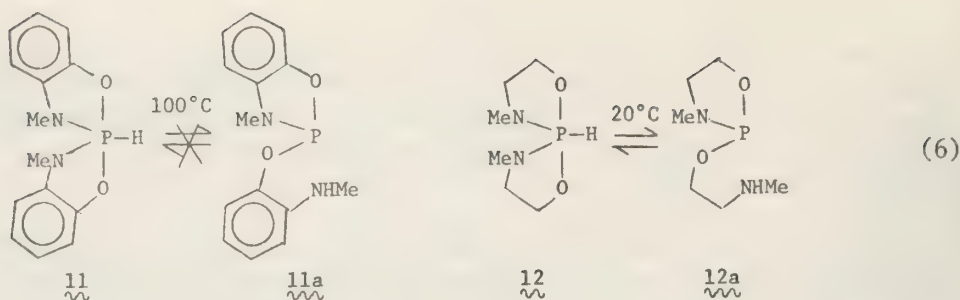


in the five-membered ring α to an apical oxygen increases the percentage of the P(V) tautomer at equilibrium, as compared to the unsubstituted phosphorane, while a carbonyl β to the apical oxygen has a destabilizing effect,^{6d} as in Eq. 5.

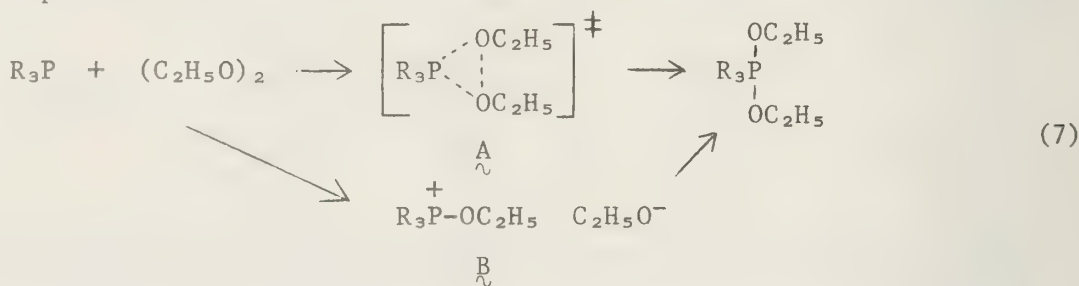


Basic or very polar solvents such as $(\text{NMe}_2)_3\text{P}=\text{O}$ can displace the P(III)-P(V) equilibrium toward the P(III) tautomer by solvation of the resultant hydroxylic or amine proton.

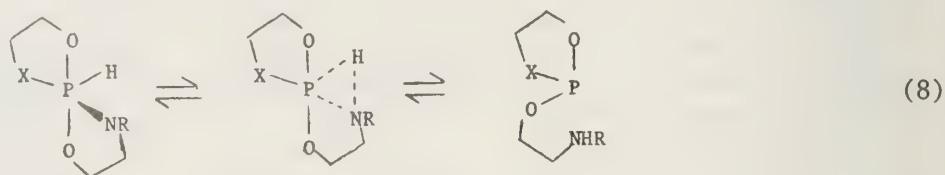
The presence of a cis double bond in the spiro rings provides a stabilization of the P(V) species. For example, the P(III) tautomer $11a$ of spiroposphorane 11 is not observable at 100°C by ^{31}P nmr, but at 20°C , 12 and $12a$ are in equilibrium, with an equilibrium composition of 10% of 12 and 90% of its P(III) tautomer, $12a$,¹¹ as shown in Eq. 6.



D. B. Denney and his colleagues have demonstrated that trivalent phosphorus compounds often react with diethyl peroxide to give phosphoranes,¹² in non-hydroxylic media through transition state \tilde{A} in Eq. 7 involving direct insertion into the weak oxygen-oxygen peroxide bond, and in a THF-H₂O medium through a likely ion-pair, \tilde{B} . Denney has dubbed the direct insertion as "biphilic", in which the trivalent phosphorus species acts as the biphile, a substance which can donate and accept a pair of electrons. He noted that further examples of potential biphiles might include carbenes and nitrenes, sulfides, and a large variety of transition metal compounds.

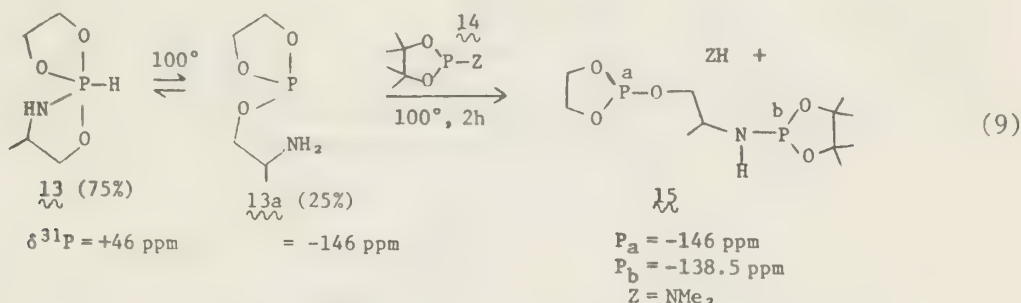


One can therefore envision a reversible biphilic insertion mechanism as one of the many unproven possibilities to explain the P(III)-P(V) tautomeric transformation, as shown in Eq. 8.

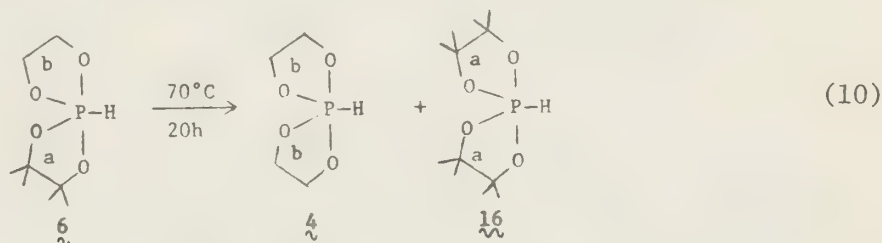


As previously mentioned, ¹H and ³¹P nmr have demonstrated for a large variety of P-H spiroposphoranes that only one P(III) tautomer is observed in equilibrium with its P(V) form. The P(III) species obtained by the opening of one of the rings of the phosphorane releases an XH nucleophile, which can attack a P(III)-Z bond, as shown in Eq. 1 (XH = OH, Z = NMe₂). An equilibrium between P(V) and P(III) tautomers could be continuously displaced to the P(III) species in the presence of a phospholane such as 14 by blocking the XH function through formation of a X-P bond, with elimination of ZH.⁸ This reaction might be used as a test for the presence of a P(III)-P(V) tautomeric equilibrium, if it could be established that no reaction of the added phospholane occurs directly with the P(V) tautomer. Several observations lend credence to this proposition. The rate of breaking of a P(III)-N bond by an attack of the nucleophile NH increases with NH basicity.¹³ An IR study has shown that in solution, spiroposphoranes derived from an aminoalcohol show an NH basicity near that of pyrrole in the P(V) tautomer;¹⁴ the rupture of one of the spiro rings in such a phosphorane occurs between phosphorus and nitrogen, with the forma-

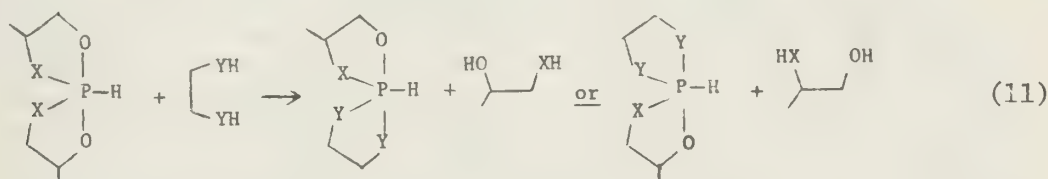
tion of a chain, the NH function regaining the basicity of normal amines. It is possible, therefore, that the phospholane would react more rapidly with the P(III) tautomer than with the P(V) tautomer, perhaps exclusively with the P(III) form, even though the P(III) form may be present in only trace quantities.



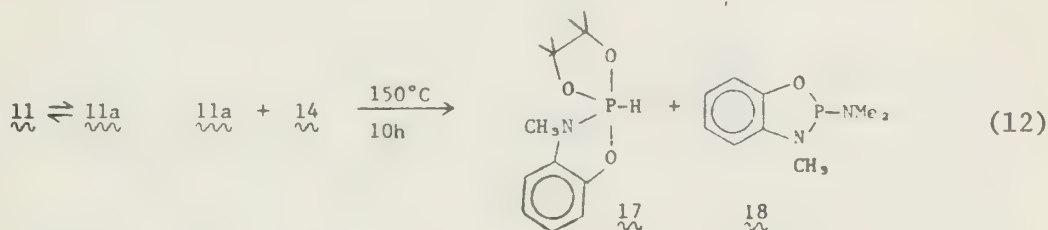
Ligand Exchange Reactions. Spirophosphoranes composed of two different rings a and b can thermally disproportionate into two symmetrical spirophosphoranes, aa and bb, as in Eq. 10.^{11a}



Ligand exchange reactions are also observed during the course of a synthesis, as in Eq. 11.^{7b}

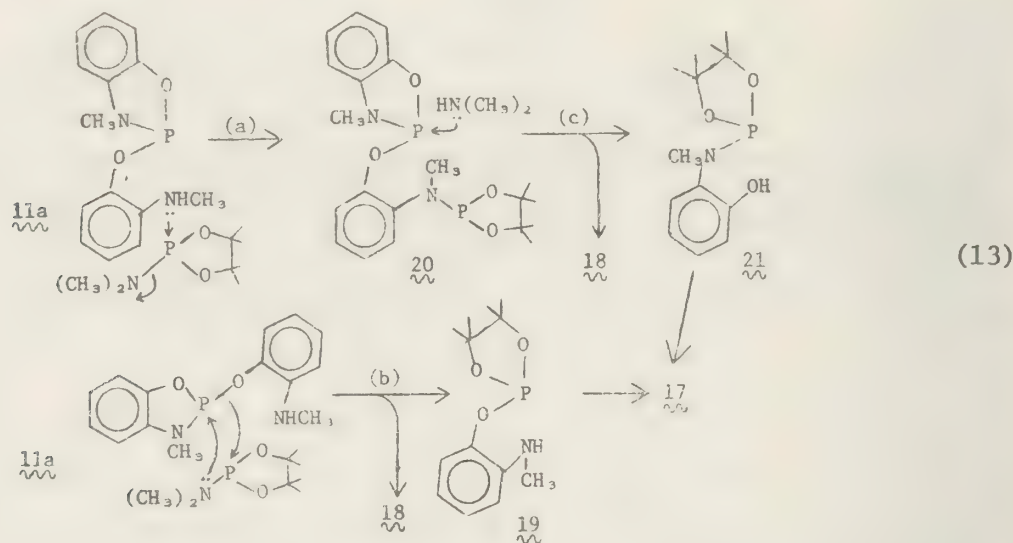


Ligand exchange has also been observed between spirophosphoranes and phospholane derivatives, as shown in Eq. 12.^{8,15} This exchange reaction

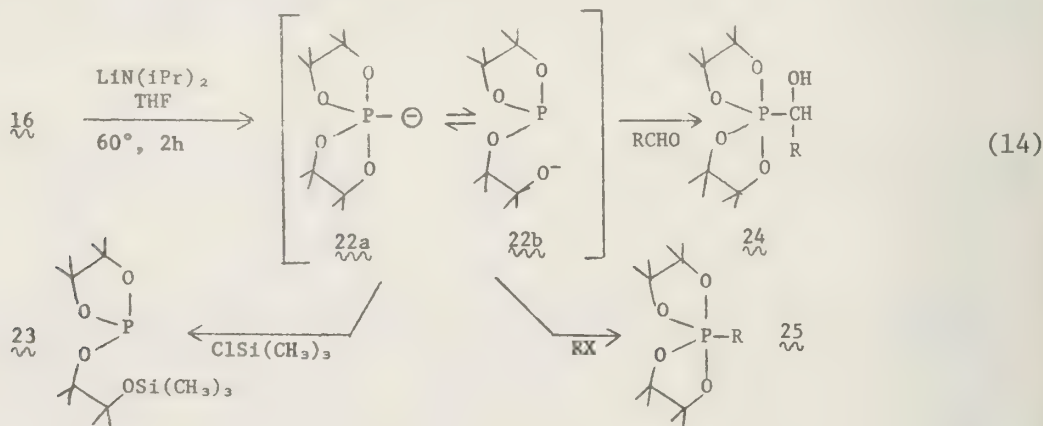


might be considered as resulting from a permutation of ligands between P(III) species, recalling in general the case of redistributions in phosphite derivatives.¹⁶ Two pathways are possible, as in Eq. 13.¹⁷ Route (a)-(c) is preferred if the amine functionality in **11a** is sufficiently nucleophilic, while (b) is followed if the added phospholane amine group is sufficiently labile. In both cases, the phosphorane equilibrates with its P(III) tautomer before reacting with the added phospholane. Pathway (a) is always the one seen for azaspirophosphoranes with an unsubstituted nitrogen (as in Eq. 9) and tetraalkoxyspirophosphoranes; evidently, for these phosphoranes, reaction of the X-H nucleophile ($\text{X} = \text{O}$,

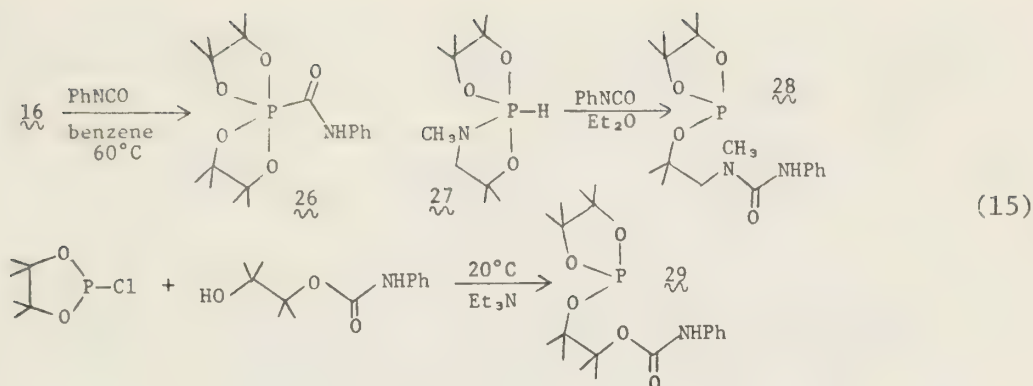
NH) in the P(III) form is more rapid than ligand exchange via route (b). Alcoholysis of a P(III)-N bond is a very fast reaction, faster than aminolysis by a primary amine; secondary amines are not sufficiently basic to make aminolysis competitive with ligand exchange. P-H phosphoranes with a free secondary amine group at the end of the chain in the P(III) tautomer always react via pathway (b). Reaction through (c) can be precluded by the fact that the reaction mixture was swept by N₂ at high temperature, which would have removed any dimethylamine produced from (a), and left 20; however, no 20 was observed, ruling out pathway (a)-(c) as the route for the observed transformation in Eq. 12.



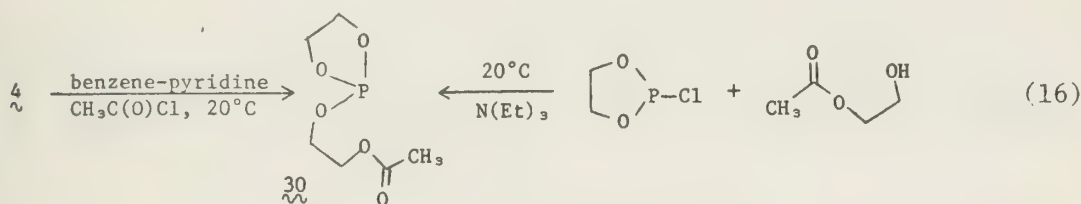
Synthetic Reactions of P-H Phosphoranes. The proton ligand of P-H phosphoranes can be liberated as H⁺ in the presence of strong bases such as NaH, NaNH₂, or LiN(iPr)₂¹⁸ at room temperature. The structure of the intermediate anion is unknown but may be represented as a mixture of 22a and 22b. Treatment of the metallated intermediate with chlorotrimethylsilane produces exclusively O-alkylated product, such as 23,¹⁸ while aldehydes react to form α-hydroxy phosphoranes such as 24 and alkyl halides react to form phosphoranes such as 25¹⁹ as shown in Eq. 14.



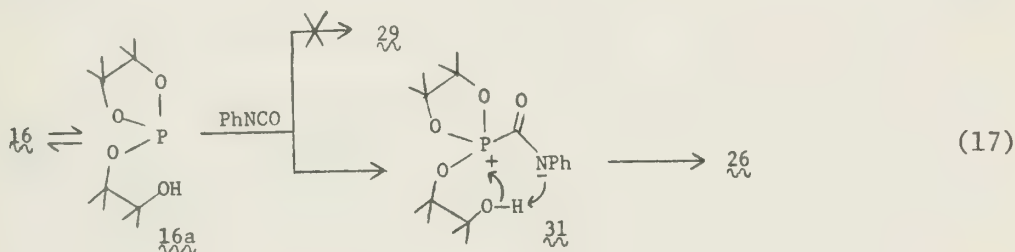
Phenyl isocyanate reacts with tetraoxyphosphoranes to form P(V) compounds such as 26 and not P(III) compounds such as 29. Carbamate 29 is stable, not rearranging after 4 days at 100°C to the spirophosphorane,²⁰ indicating that it is not an intermediate in the reaction. However, phosphoranes such as 27 form only ureas such as 28.



P-H spirophosphoranes react with acid chlorides, with opening of one of the rings of the phosphorane,^{19,21} producing esters such as 30 in Eq. 16.



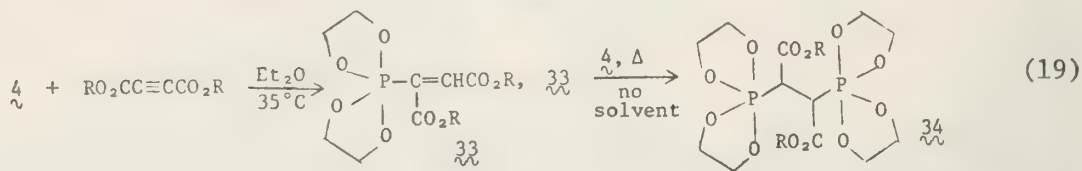
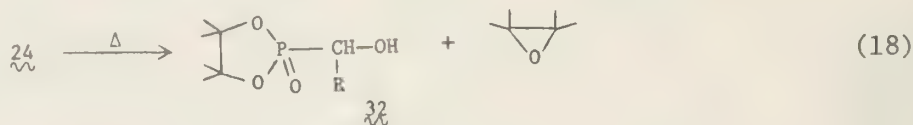
In the trimerization of isocyanates catalyzed by trialkyl phosphites, Hudson *et al.*²² proposed a mechanism in which the first step might be represented as $(RO)_3P + PhNCO \longrightarrow (RO)_3\overset{+}{P}-\overset{O}{\parallel}{C}-NPh$. One can therefore envision an intermediate such as 31 in which a negative charge on nitrogen abstracts a hydroxyl proton with concomitant ring closure, as in Eq. 17.



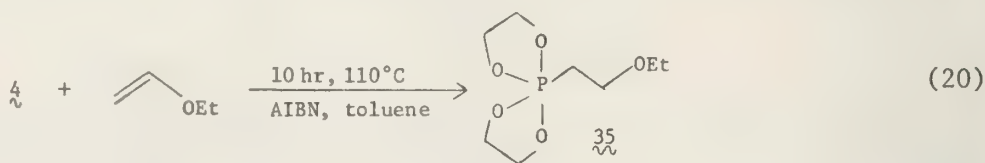
Formation of 26 and not of 29 shows that the attack of the P nucleophile of the P(III) tautomer on the isocyanate is much more rapid than the formation of a carbamate through reaction of the hydroxyl group and the isocyanate. It is well known that reactions of amines with isocyanates, with the formation of ureas, are reactions much more rapid than reactions involving alcohols, forming carbamates. It is therefore not surprising that spirophosphoranes with a free -NHR function in the P(III) tautomer form ureas rather than substituted spirophosphoranes. One cannot, however, fully rule out a mechanism involving a direct reaction of the P(V) tautomer with the isocyanate.

Aldehydes add to tetraoxy and mixed azaoxy spirophosphoranes directly, without solvent²³ or in THF after metallation.¹⁸ The compound obtained is an α -hydroxy spirophosphorane, which is thermally unstable, producing α -hydroxy phosphonates, such as 32, upon heating. Protection of the α -hydroxy group (as the silyl ether) considerably slows down the rate of thermal decomposition. Like aldehydes, imines and amins add across the P-H bond reversibly, with formation of α -amino spirophosphoranes,^{21,24}

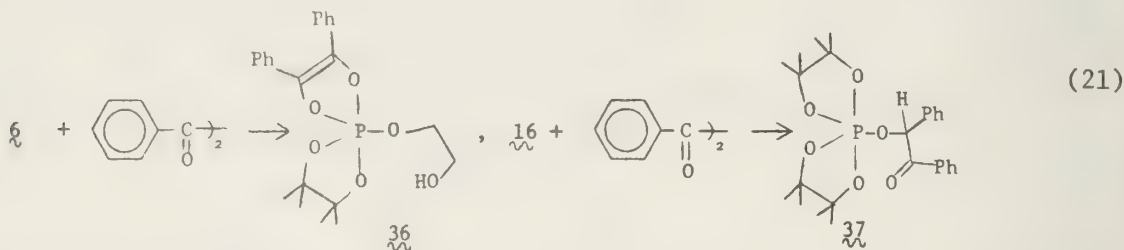
and thermally decompose into α -amino phosphonates.²¹ P-H spiroposphoranes also react with acetylene dicarboxylic esters at moderate temperatures, forming derivatives such as **33** and **34**.²⁶



P-H spiroposphoranes also react with olefins in the presence of AIBN at high temperatures, as shown in Eq. 20.²⁵ The fact that the reaction will proceed to the indicated products only in the presence of radical initiator AIBN points to a radical mechanism in the transformation.



P-H spiroposphoranes with an appreciable percentage of the P(III) tautomer react with diketones²⁸ to form spiroposphoranes such as **36**, whereas spiroposphoranes with no detectable P(III) tautomer at high temperatures react with diketones in another manner to form derivatives such as **37**, as shown in Eq. 21.



BIBLIOGRAPHY

1. (a) L. Anshutz and W. Broecker, *Chem. Ber.*, **61**, 1246 (1928); (b) R. Burgada, *Ann. Chim.*, **8**, 347 (1963); (c) L. V. Nesterov, R. A. Sabirova, N. E. Krepishcheva, and R. I. Mutalapova, *Dokl. Akad. Nauk. S.S.R.*, **148**, 1085 (1963).
2. R. Burgada, *Phosphorus and Sulfur*, **2**, 237 (1976).
3. R. Burgada, D. Houalla, and R. Wolf, *C. R. Acad. Sci.*, **264C**, 356 (1967).
4. R. R. Holmes and J. A. Dieters, *J. Chem. Res. (S)*, 92 (1977); M. G. Newton, J. E. Collier, and R. Wolf, *J. Am. Chem. Soc.*, **96**, 6888 (1974).
5. E. L. Muettert, W. Mahler, and R. Schmutzler, *Inorg. Chem.*, **2**, 613 (1963); E. L. Muettert, *J. Am. Chem. Soc.*, **91**, 1636 (1969); R. R. Holmes and R. M. Deiters, *J. Am. Chem. Soc.*, **90**, 5021 (1968).

6. (a) M. Koenig, A. Munoz, and R. Wolf, *Bull. Soc. Chim. Fr.*, 4185 (1971); (b) M. Sanchez, R. Wolf, R. Burgada, and F. Mathis, *ibid.*, 773 (1968); M. Sanchez, J. F. Brazier, D. Houalla, and R. Wolf, *ibid.*, 3930 (1967); M. Sanchez, L. Beslier, and R. Wolf, *ibid.*, 2778 (1969); M. Sanchez, L. Beslier, J. Roussel, and R. Wolf, *ibid.*, 3053 (1969); J. Ferekh, J. J. Brazier, A. Munoz, and R. Wolf, *C. R. Acad. Sci.*, 270 (1970); D. Houalla, J. F. Brazier, M. Sanchez, and R. Wolf, *Tetrahedron Lett.*, 2969 (1972); M. Gallagher, A. Munoz, G. Gence, and M. Koenig, *J. Chem. Soc., Chem. Commun.*, 321 (1976); (c) A. Munoz, M. Koenig, B. Garrigues, and R. Wolf, *C. R. Acad. Sci.*, 274C, 1413 (1972); (d) B. Garrigues, A. Munoz, M. Koenig, M. Sanchez, and R. Wolf, *Tetrahedron*, 33, 635 (1977); (e) D. Houalla, F. Osman, M. Sanchez, and R. Wolf, *Tetrahedron Lett.*, 3041 (1977).
7. (a) N. P. Greshkin, R. R. Shagidullin, and G. S. Guhanova, *Izvest. Akad. Nauk S.S.S.R.*, 8, 1797 (1968); (b) H. Germa, M. Willson, and R. Burgada, *C. R. Acad. Sci.*, 270C, 1426 (1970); R. Burgada, H. Germa, M. Willson, and F. Mathis, *Tetrahedron*, 27, 5833 (1971).
8. (a) D. Bernard, C. Laurencio, and R. Burgada, *J. Organomet. Chem.*, 47, 113 (1973); (b) R. Burgada and C. Laurencio, *ibid.*, 66, 255 (1974).
9. D. Houalla, M. Sanchez, L. Beslier, and R. Wolf, *Org. Mag. Res.*, 3, 45 (1971); R. Burgada, *Bull. Soc. Chim. Fr.*, 136 (1971).
10. R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, 107, 1080 (1915); C. K. Ingold, *ibid.*, 119, 305 (1921).
11. (a) R. Burgada, *Bull. Soc. Chim. Fr.*, 407 (1975); (b) F. Ramirez and I. Ugi, *Bull. Soc. Chim. Fr.*, 453 (1974); P. Gillespie, P. Hoffman, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 12, 91 (1973).
12. D. B. Denney, D. Z. Denney, B. C. Chang, and K. L. Marsi, *J. Am. Chem. Soc.*, 91, 5243 (1969); D. R. Denney and D. H. Jones, *ibid.*, 91, 5821 (1969); D. B. Denney, D. Z. Denney, C. D. Hall, and K. L. Marsi, *ibid.*, 94, 245 (1972); other unpublished work.
13. L. Lafaille, F. Mathis, and R. Burgada, *C. R. Acad. Sci.*, 270C, 1138 (1970).
14. F. Mathis, R. Burgada, and M. Sanchez, *Spectrochim. Acta*, 25A, 1201 (1969).
15. C. Laurencio and R. Burgada, *C. R. Acad. Sci.*, 275C, 237 (1972).
16. (a) J. R. Van Wazer and L. Maier, *J. Am. Chem. Soc.*, 86, 811 (1964); (b) J. Reiss, *Ann. Acad. Sci. N.Y.*, 159, 174 (1969); (c) R. Burgada, H. Germa, and M. Willson, *Tetrahedron*, 29, 727 (1973).
17. R. Burgada, *Internat. Colloq. of C.N.R.S.*, no. 182, 27 (1969).
18. R. Burgada, 5th All Union Conference on the Chemistry of Organophosphorus Compounds of U.S.S.R., Moscow, June 26-30, 1972.
19. P. Savignac, Y. Leroux, and R. Burgada, *J. Organomet. Chem.*, 93, 321 (1975).
20. C. Laurencio and R. Burgada, *Tetrahedron*, 32, 2089 (1976).
21. C. Laurencio and R. Burgada, *Bull. Soc. Chim. Fr.*, in press.
22. R. F. Hudson and C. Brown, *Accounts Chem. Res.*, 5, 204 (1972); C. Brown, R. F. Hudson, V. T. Rice, and A. R. Thompson, *Chem. Commun.*, 1255 (1971).
23. R. Burgada and H. Germa, *C. R. Acad. Sci.*, 267C, 270 (1968).
24. C. Laurencio, D. Bernard, and R. Burgada, *C. R. Acad. Sci.*, 278C, 1301 (1974).
25. C. Laurencio and R. Burgada, *Tetrahedron*, 32, 2253 (1976).
26. R. Burgada, *C. R. Acad. Sci. Paris*, 282, 849 (1976).
27. B. Griller and B. P. Roberts, *J. Organomet. Chem.*, 42, C47 (1972).
28. D. Bernard and R. Burgada, *C. R. Acad. Sci.*, 277C, 433 (1973).

CONCERTED ORBITAL SYMMETRY FORBIDDEN REACTIONS

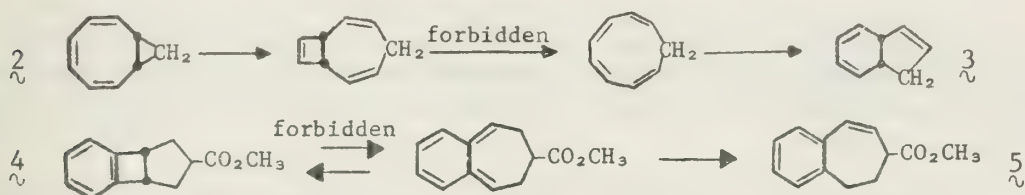
Reported by William J. Zajdel

November 10, 1977

The formulation of the Woodward-Hoffman (WH) rules was the first systematic attempt to rationalize and predict the stereoselectivity of concerted pericyclic reactions.¹⁻⁴ The most concise form of the rules is the statement "orbital symmetry is conserved in concerted reactions."⁴ A logical corollary, which has achieved wide acceptance, is that a process which does not conserve orbital symmetry must proceed in a non-concerted stepwise fashion involving intermediates. In spite of the assertion of the authors--"Violations--There are none!"³--in recent years an increasing number of experimental observations seem to be in direct conflict with Woodward and Hoffmann's theoretical predictions. A number of such contradictions are listed below. Later theoretical attempts to explain them will be discussed.

The earliest example of a possible concerted forbidden reaction, acknowledged by even Woodward and Hoffmann,³ was the disrotatory cleavage of derivatives of Dewar benzene (1) to the corresponding benzenoid compounds. Since 1 is strained ca. 60 kcal mol⁻¹ relative to benzene,⁵ it was thought to be of sufficiently high energy to overcome the additional 37 kcal mol⁻¹ barrier⁶ of the forbidden pathway.⁴

The facile thermal isomerization of cis-bicyclo[6.1.0]nona-2,4,6-triene (2) to cis-3a,7a-dihydroindene (3) is proposed to proceed via a forbidden opening,¹⁰ as is the isomerization of 4 to 5.¹¹



Recently a $4\pi + 2\sigma + 2\sigma$ photochemically forbidden cycloaddition was reported involving the addition of anthracene, acridine or tetrachloro-o-benzoquinone and quadricyclane (6).¹²

The most convincing experimental evidence for the existence of concerted forbidden processes is the elegant study of the thermolysis of trans-1,2-trans,trans-dipropenylcyclobutane (7) and the trans,cis,trans analogue (8). The resultant products by antarafacial or suprafacial migration with retention or inversion for 7 are shown below. The experimental results are in Table 1.¹³

The inversion/retention ratios (si + ai/sr + ar) are 51.6:48.4 for 7 and 49.5:50.5 for 8, which suggests random stereochemistry resulting from a planar diradical intermediate with internal rotation which is fast relative to ring closure. A closer look shows only 12% of the antarafacial products for 7 and 5.5% for 8, which rules out the possibility of randomness due to a planar diradical. The results can best be explained by competition between stereospecific suprafacial migrations, namely, concerted allowed and forbidden processes.

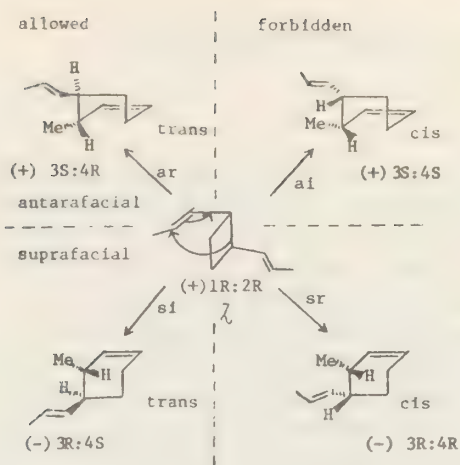


Table 1

Reactant	Rel. Ratios of Product Formation			
	Allowed		Forbidden	
	si	ar	sr	ai
$\begin{smallmatrix} 7 \\ \diagup \\ 8 \end{smallmatrix}$	50.8	5.4	43.0	0.8
$\begin{smallmatrix} 8 \\ \diagdown \\ 7 \end{smallmatrix}$	49.5	2.7	47.8	0

The earliest attempt to explain the occurrence of WH forbidden reactions by a concerted mechanism was by Braumann and Golden.^{14,15} Their study led to the conclusion that product stereochemistry was not an adequate measure of orbital symmetry transition state stabilization for strained systems.

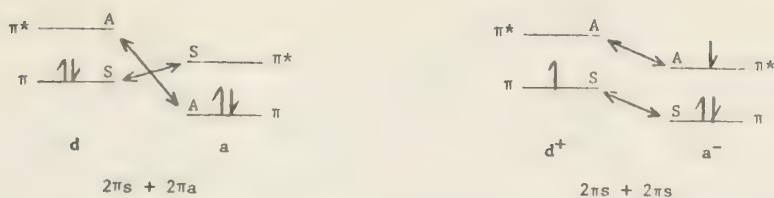
The first attempt at a general theory of cycloaddition reactions, which concluded that both WH allowed and forbidden reactions may be concerted, was proposed by Epiotis.¹⁶⁻¹⁹ He noted that WH rules could be applied successfully only to nonpolar systems.²⁰ By extending considerations to polar systems, Epiotis extended the scope of symmetry rules to include formerly forbidden reactions.

For the general case of a π - π cycloaddition involving a doubly occupied MO (M) of polyene A interacting with an unfilled MO (N) of polyene B, and that of a doubly occupied MO (K) of B interacting with an unfilled MO (L) of A, Epiotis defines the total stabilization of the interactions as:

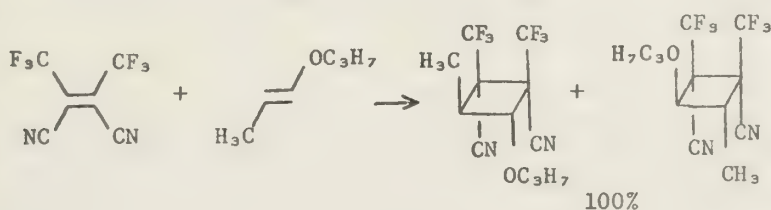
$$SE = 2[(a_{Mr}b_{Ns} + a_{Mt}b_{Nu})^2\gamma^2(E_M - E_N)^{-1}] + [(a_{Lr}b_{Ks} + a_{Lt}b_{Ku})^2\gamma^2(E_K - E_L)^{-1}]$$

where E_N represents the energy level of MO (N), a_{Mr} is the coefficient of the r th p atomic orbital of polyene A belonging to wave function M and γ stand for the resonance integral between the two interacting p atomic orbitals at the union sites. It follows that the stabilization energy will depend on (1) the proximity of the interacting energy levels ($E_M - E_N$ and $E_K - E_L$), (2) the phase compatibility of the interacting MO's ($a_{Mr}b_{Ns} + a_{Mt}b_{Nu}$ and $a_{Lr}b_{Ks} + a_{Lt}b_{Ku}$), and (3) the geometry of the transition state, i.e., the nature of orbital overlap (γ). WH rules deal exclusively with the second factor, phase compatibility, with the exclusion of the other two. Predictions of cycloaddition pathways via correlation diagrams relating only orbital symmetry and not energies and geometries, therefore, can not be general.

A redefinition of cycloadditions in terms of donors and acceptors, where cycloaddend 1 is the donor and 2 the acceptor, i.e., $E_{HOMO\ 1} - E_{LUMO\ 2} < E_{HOMO\ 2} - E_{LUMO\ 1}$, can lead to different stereochemical predictions than the WH rules, since in a highly polar system, the transition state is better described by a resonance hybrid involving charge-transfer ($d^+ \cdots a^-$) than a no-bond ($d \cdots a$) contributing structure. An example of the importance of the charge-transfer (CT) contribution in the transition state can be seen in polar $2\pi + 2\pi$ cycloadditions. Correlation diagrams for the no-bond (NB) and CT transition states are shown below. Strong interactions are denoted by arrows.

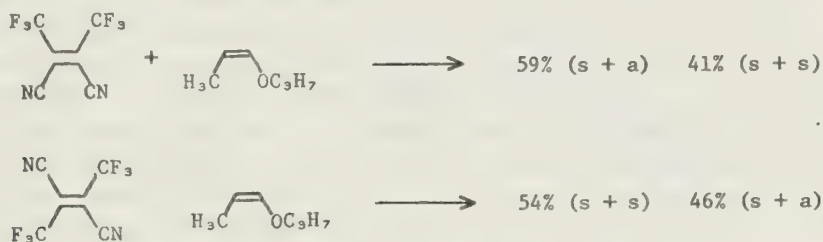


While phase correlation stabilizes the $s + a$ transition state slightly more than the $s + s$ transition state, orbital overlap is highly favored for the latter transition state. For the reaction of unsubstituted ethylenes $\gamma s + s/\gamma s + a$ has been calculated as 12.5.¹⁶ Substituted ethylenes have the added ability of electrostatic attractions which are greater in the parallel $s + s$ transition state relative to the perpendicular $s + a$ transition state. This should further increase the favorability of orbital overlap in the $s + s$ transition state. Indeed model calculations have shown that orbital overlap effects far outweigh energy level proximity for polar $2\pi + 2\pi$ cycloadditions, which are predicted, therefore, to occur in a $2\pi s + 2\pi s$ concerted, WH forbidden manner. Over twenty-five examples of such reactions, having $s + s$ products in excess of 90% have been found,²¹ including the following:^{22,23}

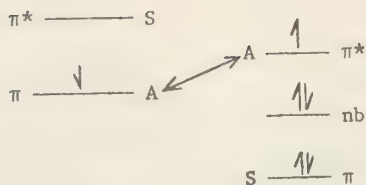


Theoretical calculations have shown that donor-acceptor (DA) interactions involving CT in the transition state can also explain $2s + 2s$ additions involving reactive species such as singlet oxygen and benzyne.^{24,25}

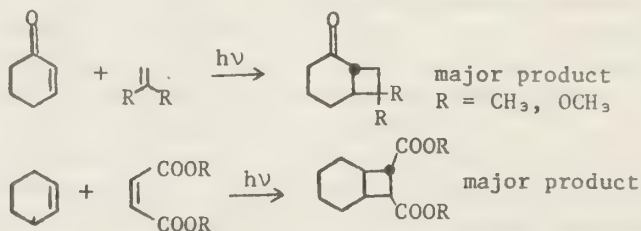
If the $2\pi s + 2\pi a$ and $2\pi s + 2\pi s$ reactions are of similar energy in a polar system, the reactions will naturally compete. Such apparent nonstereoselectivity has given credence to diradical or dipolar pathway postulates. DA theory postulates, however, that only the acceptor addend will rotate due to π bond weakening caused by increased π^* character, whereas dipolar or diradical intermediates should lead to rotation in either cycloaddend. Donor-acceptor theory has been supported by the results shown below. In both cases acceptor rotation was exclusively found in $2s + 2a$ products.²⁷



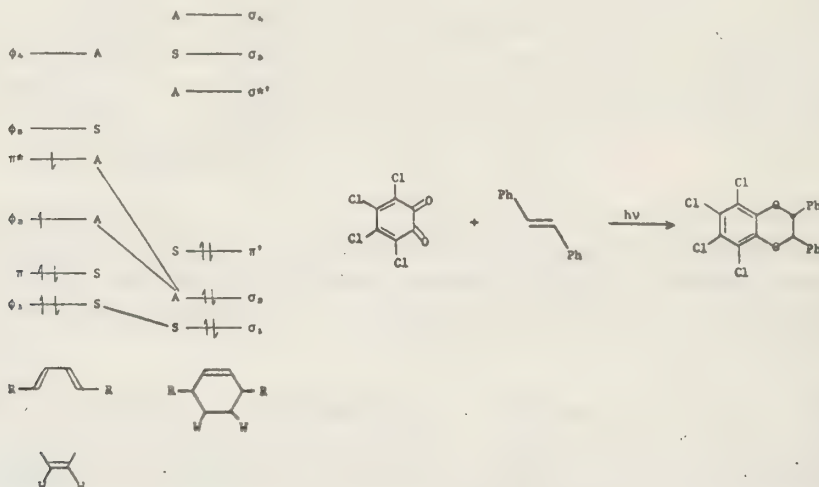
WH forbidden photochemical reactions can also be treated with DA analysis. Polar $2\pi + 2\pi$ cycloadditions have been found to proceed in a $2s + 2a$ forbidden fashion. A correlation diagram for a CT interaction of a donor and $n-\pi^*$ excited acceptor cycloaddition is shown below.¹⁸



The observed $s + a$ stereoselectivity results from the strong interaction denoted by the arrows. Examples of such reactions include:²⁸⁻³⁰

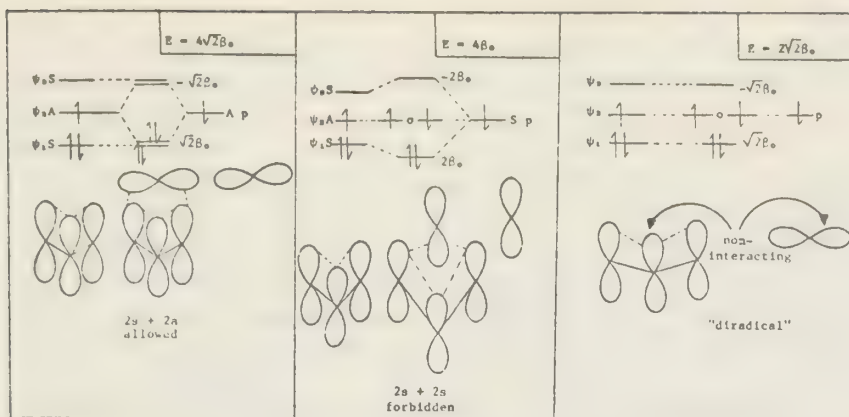


Polar $2\pi + 4\pi$ photocycloadditions also are predicted by DA theory to occur by WH forbidden $4\pi_s + 2\pi_s$ pathways. A correlation diagram for a CT transition state of an excited dieneophile is shown.^{19,20}

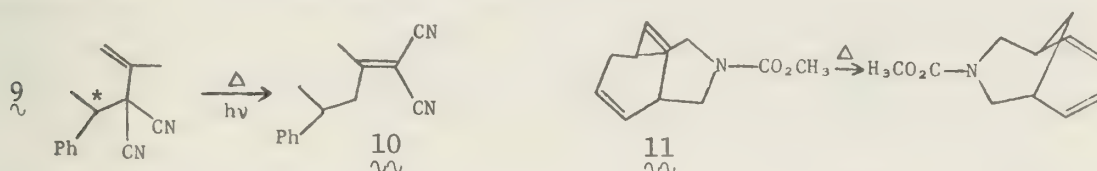


For polar photocycloadditions, stabilization due to proximity, phase compatibility and favorable geometry all favor the $2\pi_s + 4\pi_s$ reaction. An example of such a reaction is shown above.³¹

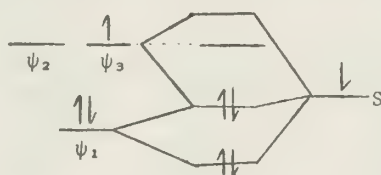
Another theory suggested by Berson and Salem attempts to explain the occurrence of concerted WH forbidden reactions by invoking subadjacent orbital interactions to stabilize forbidden transition states.^{32,33} Schematic orbital correlation diagrams for suprafacial 1,3 allowed, forbidden and diradical sigmatropic rearrangements are shown below. The stabilization energies are $4\sqrt{2}\beta_0$, $4\beta_0$, and $2\sqrt{2}\beta_0$, respectively. Stabilization of the forbidden transition state arises not from interactions of the p orbital with the allyl HOMO, but rather the subadjacent symmetrical bonding π orbital. This stabilization, which exceeds that for the diradical process, could become quite important if the allowed pathway were sterically blocked. Theoretical calculations have shown that subadjacent orbital control is indeed an important factor in nonpolar and semipolar shifts.³⁴ A report of a 1,3 forbidden thermal sigmatropic shift proceeding with retention is that of 3,3-dicyano-2-methyl-4-phenylpent-1-ene (9) to 1,1-dicyano-2-methyl-4-phenylpent-1-ene (10). The photochemical isomerization was found to



proceed with ca. 85% retention of configuration at the migrating center, as predicted by WH rules, but the thermal isomerization proceeded with greater than 90% retention, in direct violation.³⁵

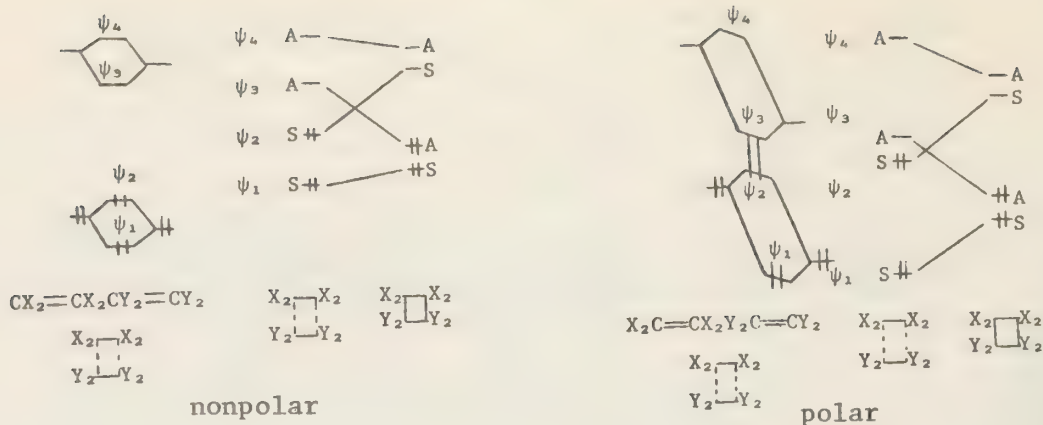


Another reported 1,3-suprafacial shift with retention is the thermal rearrangement of N-carbomethoxy-3-azabicyclo[3.3.2]deca-6,9-diene (11). Deuterium labeling studies of the protons adjacent to the nitrogen atom revealed that the reaction proceeded with net retention.³⁶ Berson and Holder have found allowed and forbidden pathways to compete in several bicyclic systems, the forbidden ones being favored if the geometry for inversion is unfavorable.⁷⁻⁹ A recent theoretical study indicates that subadjacent orbital control is important in 1,3 hydrogen shifts in cyclopropene.³⁷ The perturbed energy levels were determined by strong interactions of the migrating group with ψ_1 and ψ_3 of cyclopropene, both of which have similar coefficients for C_1 and C_3 . The schematic energy diagram is shown below.

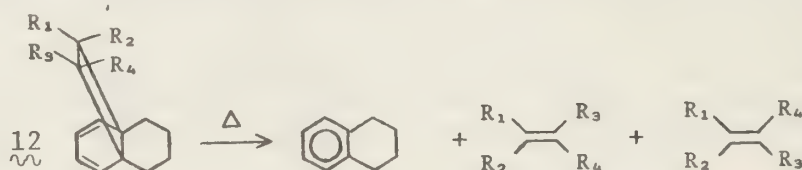


A third attempt to explain concerted forbidden reactions has been called Configurational Interaction (CI) theory.^{38,42} CI theory essentially leads to the same predictions as DA theory, but is more useful in theoretical calculations. Correlation diagrams for a nonpolar and polar $2\pi s + 2\pi s$ thermal cycloaddition are shown below.^{41,42}

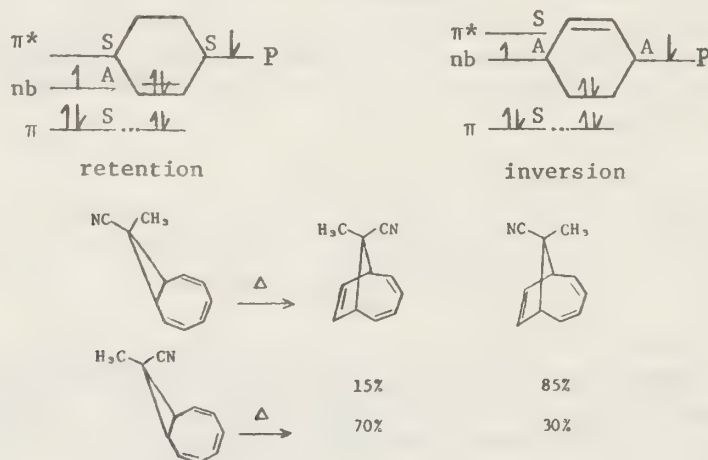
In order for this reaction to occur in a $2\pi s + 2\pi s$ fashion, two electrons would have to be promoted from ψ_2 to ψ_3 , for the transition state to correlate to the product ground state. In the nonpolar case, the energy required would be considerable, but not in the polar case. If the transition state has a strong contribution from the doubly excited state, as it should in the polar system, a $2\pi s + 2\pi s$ reaction should be expected to predominate, especially since the orbital overlap geometry ($\gamma s + s/\gamma s + a$) strongly favors the $s + s$ pathway. This prediction is supported by the study of thermal cycloreversions of [4.4.2]propella-2,4-dienes (12). Increased substitution of the two carbon bridge by electron



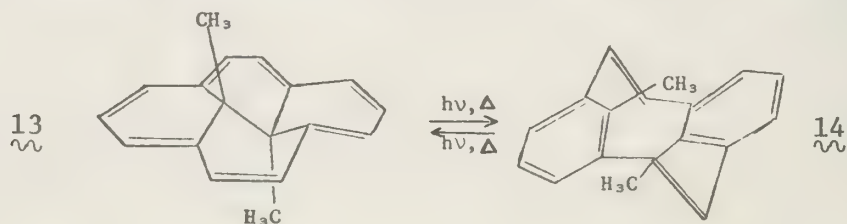
donating substituents leads to an increased preference for the $s + s$ elimination up to 95% retention.⁴³



Configurational interaction also agrees with subadjacent orbital control predictions of 1,3-suprafacial shifts with retention for nonpolar systems. Correlation diagrams for retention and inversion are shown below. Strong mixing of the ground state and diexcited configuration in the transition state, which is expected in the former case since the energies of the two configurations are comparable, would lead to strong pericyclic bonding in the forbidden reaction.³⁹ An example of predominant retention in 1,3 shifts was found by Klärner.⁴⁴

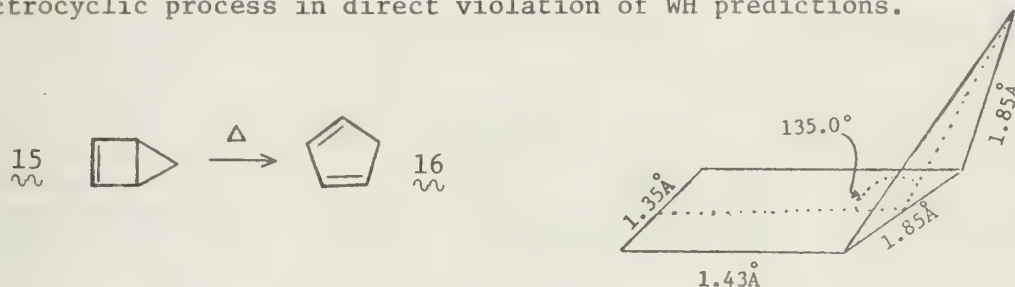


The facile interconversion of 15,16-dimethyl dihydropyrene (13) and 15,16-dimethyl[2.2]metacyclophane-4,9-diene (14) was explained in terms of CI stabilization of a forbidden transition state.^{45,46} The thermally

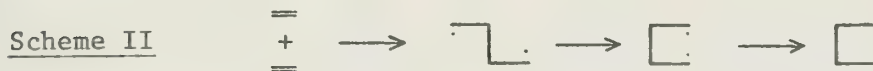


forbidden 6 or 14 electron conrotatory conversion was suggested to proceed because of strong CI due to the molecule's low-lying electronically excited states resulting from its extended π system.

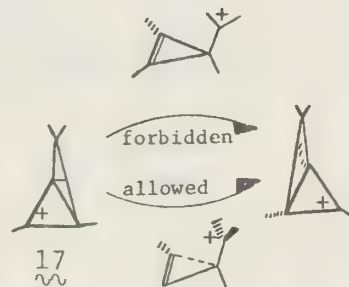
Theoretical calculations have recently been used to determine the importance of CI in nonallowed processes. A MINDO/2 study revealed that inclusion of CI has no detrimental effects, but rather improves thermodynamic calculations for normal molecules, and indeed improves calculations for forbidden processes.⁴⁷ Recently CI has been utilized in theoretical energy calculations for forbidden ring openings of cyclopropene,⁴⁸ cyclobutene,^{49,50} and cyclopentenes.^{51,52} The energy difference between conrotatory and disrotatory ring cleavages in cyclobutene is calculated as 100 kcal mol⁻¹ according to valence bond estimates, 49 kcal mol⁻¹ from self consistent field calculations, but only 13.6 kcal mol⁻¹ when CI calculations are included in the SCF functions.⁴⁹ The latter study predicts a totally symmetric transition state using MINDO/3 calculations, as shown below, for the conversion of 15 to 16.⁵¹ The results indicate that the conversion is a concerted electrocyclic process in direct violation of WH predictions.



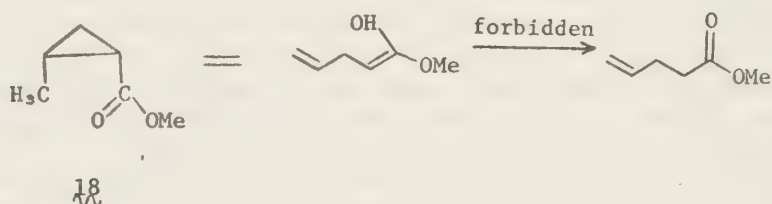
An extensive theoretical treatment, which included CI for $2\pi + 2\pi$ thermal cycloadditions, using Mulliken-Wolfsberg-Helmholtz, SCF-MO-CNDO/2 and STO-4G ab initio calculations has led to the conclusion that forbidden polar $2\pi_s + 2\pi_s$ cycloadditions do indeed occur in a concerted-like process with an early low barrier to pericyclic bonding (Scheme I), whereas the WH allowed nonpolar $2\pi_s + 2\pi_a$ process is actually a diradical process with a late high energy barrier to pericyclic bonding (Scheme II).⁵²



Theoretical calculations have also been used to predict forbidden reactions which have not yet been observed. The forbidden thermal rearrangement of 17 has been calculated to be energetically favored by more than 30 kcal/mol⁻¹ over the allowed transition due to overlap with the cyclopropyl Walsh orbitals.^{53,54}



A general theoretical treatment of forbidden reactions has been outlined by George and Ross. They note that WH rules can be destroyed by distortions in the transition state due to vibrations of the nuclei involved.⁵⁵ A similar treatment of catalyzed symmetry forbidden reactions has been presented by Ferreira.⁵⁶ Examples of forbidden reactions that can occur only if catalyzed include the isomerization of substituted Dewar pyridines to pyridines,⁵⁷ and the thermolysis of methyl-cis-2-methylcyclopropanecarboxylate (18), which was found to occur on the surface of gas phase reactors.⁵⁸



At present there is actually little definitive evidence that WH forbidden reactions are concerted. Because they are so far ill-defined, diradicals can be used to rationalize, a posteriori, any observation, including WH allowed reactions. By invoking diradicals or dipolar intermediates almost any set of chemical data can be rationalized. By invoking concerted donor-acceptor, subadjacent orbital control and/or configurational interaction theories, however, great predictive power can be realized, and, to date, experimental results are in good agreement with such predictions.

BIBLIOGRAPHY

1. R. B. Woodward and R. Hoffmann, J. Am. Chem. Soc., 87, 395 (1969).
2. R. B. Woodward and R. Hoffmann, Acc. Chem. Res., 1, 17 (1968).
3. R. B. Woodward and R. Hoffmann, Angew. Chem., 81, 797 (1969); Angew. Chem., Int. Ed. Engl., 8, 781 (1969).
4. R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970.
5. W. Schäfer, Angew. Chem., 78, 716 (1966); Angew. Chem., Int. Ed. Engl., 5, 669 (1966).
6. J. Oth, Angew. Chem., 80, 633 (1968); Angew. Chem., Int. Ed. Engl., 7, 646 (1968).
7. J. Berson and G. Nelson, J. Am. Chem. Soc., 89, 5303 (1967).
8. J. Berson and G. Nelson, J. Am. Chem. Soc., 92, 1096 (1970).
9. J. Berson and R. Holder, J. Am. Chem. Soc., 95, 2037 (1973).
10. J. Baldwin, A. Andrist, and R. Pinschmidt, Jr., J. Am. Chem. Soc., 94, 5845 (1972).
11. D. Weiss, Tetrahedron Lett., 4001 (1975).
12. T. Sasaki, K. Kamematsu, I. Ando, and O. Yamashita, J. Am. Chem. Soc., 99, 871 (1977).
13. J. Berson and P. Dervan, J. Am. Chem. Soc., 95, 269 (1973).
14. J. Brauman and D. Golden, Trans. Faraday Soc., 65, 464 (1969).
15. J. Brauman and D. Golden, J. Am. Chem. Soc., 90, 1920 (1968).
16. N. Epiotis, J. Am. Chem. Soc., 94, 1924 (1972).
17. N. Epiotis, J. Am. Chem. Soc., 94, 1935 (1972).
18. N. Epiotis, J. Am. Chem. Soc., 94, 1941 (1972).
19. N. Epiotis, J. Am. Chem. Soc., 94, 1946 (1972).

20. N. Epiotis and R. Yates, *J. Org. Chem.*, 39, 3150 (1974).
21. N. Epiotis, R. Yates, D. Carlberg, and F. Bernardi, *J. Am. Chem. Soc.*, 98, 453 (1976).
22. S. Proskow, H. Simmons, and T. Cairns, *J. Am. Chem. Soc.*, 88, 5254 (1966).
23. P. Bartlett and A. Schapp, *J. Am. Chem. Soc.*, 92, 3223 (1970).
24. S. Inagaki and K. Fukui, *J. Am. Chem. Soc.*, 97, 7480 (1975).
25. H. Fujimoto and T. Sugiyama, *J. Am. Chem. Soc.*, 99, 15 (1977).
26. J. Lacher, G. Tompkin, and J. Park, *J. Am. Chem. Soc.*, 74, 1693 (1952).
27. N. Epiotis, *Angew. Chem.*, 86, 825 (1974); *Angew. Chem., Int. Ed. Engl.*, 13, 751 (1974).
28. E. J. Corey, J. Bass, R. LeMahieu, and R. Mitra, *J. Am. Chem. Soc.*, 86, 5570 (1964).
29. A. Cox, P. de Mayo, and R. Yip, *J. Am. Chem. Soc.*, 88, 1043 (1966).
30. R. Robson, P. Gruble and J. Barltrop, *J. Chem. Soc.*, 2153 (1964).
31. D. Bryce-Smith and A. Gilbert, *Chem. Commun.*, 1701 (1968).
32. J. Berson and L. Salem, *J. Am. Chem. Soc.*, 94, 8917 (1972).
33. J. Berson, *Acc. Chem. Res.*, 5, 406 (1972).
34. N. Epiotis, R. Yates, and F. Bernardi, *J. Am. Chem. Soc.*, 97, 4198 (1975).
35. R. Cookson and J. Kemp, *Chem. Commun.*, 385 (1971).
36. G. Krow and J. Reilly, *J. Am. Chem. Soc.*, 97, 3837 (1975).
37. J. de Dobbelaere, J. van Dyk, J. de Haan, and H. Buck, *J. Am. Chem. Soc.*, 99, 392 (1977).
38. N. Epiotis, *J. Am. Chem. Soc.*, 95, 1191 (1973).
39. N. Epiotis, *J. Am. Chem. Soc.*, 95, 1200 (1973).
40. N. Epiotis, *J. Am. Chem. Soc.*, 95, 1206 (1973).
41. N. Epiotis, *J. Am. Chem. Soc.*, 95, 1214 (1973).
42. J. Baldwin, A. Andrist, and P. Pinschmidt, Jr., *Acc. Chem. Res.*, 5, 402 (1972).
43. L. Paquette and G. Thompson, *J. Am. Chem. Soc.*, 93, 4920 (1971).
44. F. Klärner, *Tetrahedron Lett.*, 3611 (1971).
45. W. Schmidt, *Tetrahedron Lett.*, 581 (1972).
46. W. Schmidt, *Helv. Chim. Acta.*, 54, 862 (1971).
47. R. Bingham and M. J. Dewar, *J. Am. Chem. Soc.*, 94, 9107 (1972).
48. M. J. Dewar and S. Kirschner, *J. Am. Chem. Soc.*, 93, 4291 (1971).
49. K. Hsu, R. Buenker, and S. Peyerimhoff, *J. Am. Chem. Soc.*, 93, 2117 (1971).
50. M. J. Dewar, *J. Am. Chem. Soc.*, 96, 6809 (1974).
51. N. Bodor, M. J. Dewar, and D. Lo, *J. Am. Chem. Soc.*, 94, 5303 (1972).
52. N. Epiotis, R. Yates, D. Carlberg, and F. Bernardi, *J. Am. Chem. Soc.*, 98, 453 (1976).
53. W. Hehre and A. Devaquet, *J. Am. Chem. Soc.*, 96, 3644 (1974).
54. W. Hehre and A. Devaquet, *J. Am. Chem. Soc.*, 98, 4370 (1976).
55. T. George and J. Ross, *J. Chem. Phys.*, 55, 3851 (1971).
56. R. Ferreira, *Chem. Phys. Lett.*, 41, 370 (1976).
57. Y. Kobayashi and A. Ohsawa, *Chem. Pharm. Bull.*, 24, 2225 (1976).
58. J. Gajewski, R. Weber, R. Brown, M. Manion, and B. Hymen, *J. Am. Chem. Soc.*, 99, 816 (1977).

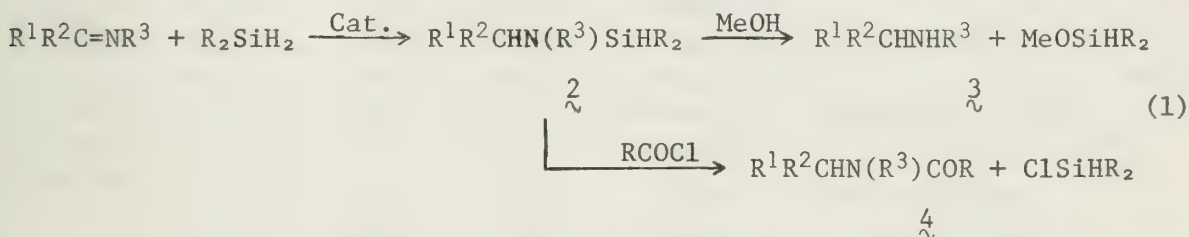
ASYMMETRIC REDUCTIONS VIA HYDROSILYLATION CATALYZED BY RHODIUM(I) COMPLEXES

Reported by Garret D. Figuly

November 14, 1977

The two primary reduction methods used most often for the reduction of various functionalities are those involving metal hydrides such as LiAlH_4 , NaBH_4 , NaBH_3CN , $\text{LiAl}[\text{OC}(\text{CH}_3)_3]_3\text{H}$, etc. and hydrogenation catalyzed by transition metals and metal complexes.¹ For some time organosilicon hydrides were not considered to be reducing agents because they are generally very stable substances virtually lacking any reducing ability.² It was discovered, however, that organosilicon hydrides can add to unsaturated bonds if a proper catalyst is added to the system.³ Thus, since silicon heteroatom bonds can be easily cleaved by the action of acids or bases,² organosilicon hydrides can be used as reducing agents if the hydrosilylation of the compounds containing such double bonds is effectively achieved.

Recently, Ojima reported the development of a powerful new method for the reduction of carbon heteroatom double bonds using catalytic hydrosilylation.⁴ When he uses a rhodium(I) complex such as tris-(triphenylphosphine)-chlororhodium (1) as the catalyst he can selectively reduce α,β -unsaturated ketones in yields greater than 90%.² Ojima also found that Schiff bases could be reduced by catalytic hydrosilylation using either 1 or PdCl_2 as the catalyst as in Eq. 1.⁵ These reactions were found to go in highest yield and very smoothly when dihydrosilanes were used. It should also be noted that the silyl-protected amine (2), which is known to be a versatile reagent in organic syntheses,⁶ can be obtained in the first step. The protected amine could then easily be converted to an amide (4) or the amine (3) by reaction with either an acyl chloride or methanol.



Similarly, isocyanates can be reduced to formamides and their derivatives⁷ while carbodiimides can be reduced to formamidines and N-acetylformamidines.⁸

While other examples can be given for the high utility of the hydrosilylation reaction for the reduction of various functionalities,⁹ an important potential for this reaction seems to lie in its ability to carry out asymmetric reductions yielding moderate to high enantiomeric excesses under very mild conditions. Thus, the use of the hydrosilylation reaction for asymmetric reductions constitutes the subject of this seminar.

Asymmetric Reductions of α -, β -, and γ -Keto Esters. One example of the use of the hydrosilylation reaction in asymmetric synthesis is in the synthesis of optically active α -hydroxycarboxylic acids. The synthesis of these optically active acids has gathered much attention for a long period of time, and a large number of reports have been made on the Grignard reaction and the reduction of α -keto esters.¹⁰ Although reductions of phenylglyoxylic acid and its esters by the use of chiral magnesium alkoxides¹¹ and LiAlH_4 chiral alcohol complexes¹² have been reported, the optical yield obtained by the former agents was 15-33% while that obtained by the latter systems was 4-17%. Ojima recently reported the asymmetric reduction of

α -, β - and γ -keto esters via hydrosilylation catalyzed by a rhodium complex with chiral phosphine ligands under very mild conditions.¹³ These reactions are illustrated in Eq. 2a-c, and some of the results are summarized in Table 1.

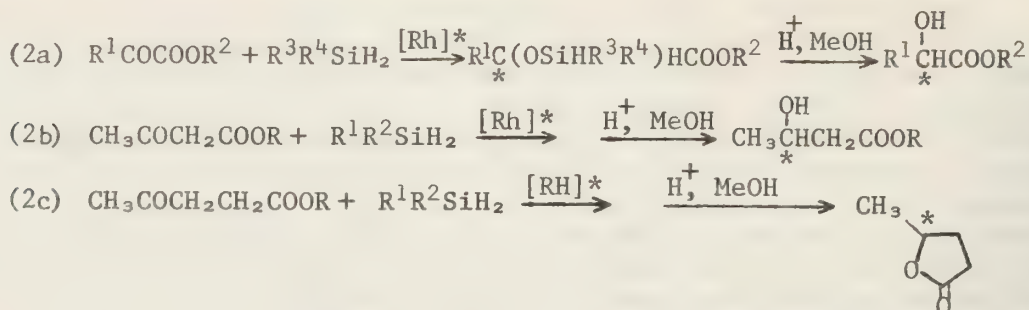
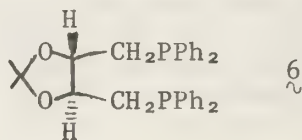
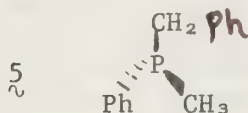


Table 1. Asymmetric Reductions of α -, β - and γ -Keto Esters Via Hydro-silylations

Ester	Hydrosilane	Chiral Ligand	Yield, %	Optical Purity, %
CH ₃ COCOOPr- <u>n</u>	Et ₂ SiH ₂	(+)-BMPP	85	30.3 (R)
	Ph ₂ SiH ₂	(+)-BMPP	84	60.3 (R)
	Ph ₂ SiH ₂	(+)-DIOP	82	76.5 (S)
	α-NpPhSiH ₂	(-)-DIOP	90	85.4 (R)
PhCOCOEt	Et ₂ SiH ₂	(+)-BMPP	80	6.4 (S)
	Ph ₂ SiH ₂	(+)-BMPP	82	10.3 (R)
	Ph ₂ SiH ₂	(+)-DIOP	80	9.7 (S)
	α-NpPhSiH ₂	(+)-DIOP	87	39.2 (S)
CH ₃ COCH ₂ COOMe	Ph ₂ SiH ₂	(+)-DIOP	84	13.7 (S)
	α-NpPhSiH ₂	(+)-DIOP	89	23.5 (S)
CH ₃ COCH ₂ COOBu- <u>n</u>	Ph ₂ SiH ₂	(+)-DIOP	83	12.0 (S)
	α-NpPhSiH ₂	(+)-DIOP	92	24.0 (S)
CH ₃ COCH ₂ CH ₂ COOMe	Ph ₂ SiH ₂	(+)-DIOP	99	39.6 (S)
	α-NpPhSiH ₂	(+)-DIOP	99	76.2 (S)
CH ₃ COCH ₂ CH ₂ COOCH ₂ Ph	Ph ₂ SiH ₂	(+)-DIOP	95	38.1 (S)
	α-NpPhSiH ₂	(+)-DIOP	100	75.1 (S)

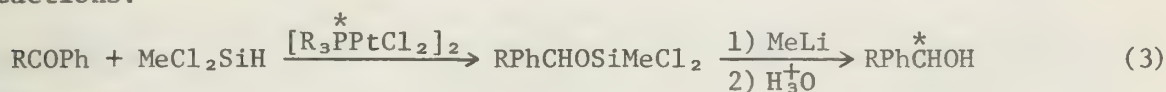
The reactions of Eq. 2a were carried out via hydrosilylation catalyzed by rhodium(I) complexes with (R)-(+)-benzylmethylphenylphosphine (BMPP) (5), and 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (DIOP) (6)¹⁴ as chiral ligands. As seen from Table 1,



optical yields depend on the nature of the hydrosilane used, and the configuration of the product derived by the use of (+)-BMPP is opposite to that derived by using (+)-DIOP. It should also be noted that in every case the combination of α -naphthylphenylsilane and DIOP ligand displayed the best results, and the optical yields obtained by this method are much higher than those obtained by other methods. (The optical yield obtained in the case of n-propyl pyruvate (85.4%) is the highest one ever observed.)¹³

The reactions of Eq. 2c are significant in that they provide a facile asymmetric synthesis of 4-methyl- γ -butyrolactone with an optical yield comparable to the 64-73% optical yields recently reported by Meyers and Mihelich¹⁵ in the asymmetric synthesis of 2-substituted γ -butyrolactones using optically active oxazolines.

Asymmetric Reductions of Ketones. One of the most highly studied fields of asymmetric reductions involving hydrosilylation is that of the reduction of simple prochiral ketones.¹⁶ The first asymmetric hydrosilylation of prochiral ketones was reported by Yamamoto^{16a} using chiral platinum complexes at room temperature (Eq. 3). His method does not give very high optical yields (<20%), however, and has the following disadvantages:^{16f} (1) the hydrosilane which can be used for the reaction is restricted to methyldichlorosilane (trialkyl silanes cannot be employed because of their lack of reactivity); (2) although the optical yield can be increased to some extent by employing bulky ketones, the chemical yields decrease markedly; and (3) only alkyl phenyl ketones are suitable for substrates since dialkyl ketones give products only in low yield and with many side reactions.



The report by Scorrano^{16d} that $[\text{Rh}(\text{PPhMe}_2)_2\text{H}_2\text{S}_2]^+$ (S = solvent) catalyzed the asymmetric reduction of simple ketones prompted Yamamoto to attempt asymmetric hydrosilylations using a similar catalyst as in Eq. 4.^{16e}



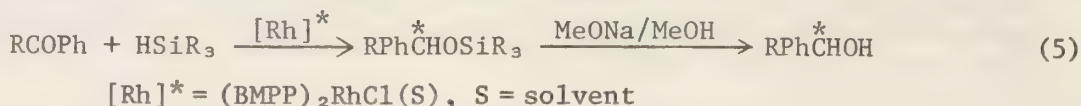
These reactions had to be run at 50°C for 40 hours using an alkyl phenyl ketone to give the results shown in Table 2. It should be noted that there is a considerable variation in optical yield with silane structure. It is also obvious from the resulting configuration of the *t*-butyl phenyl ketones using the different trialkylsilanes as hydrosilylating agents that there is a steric need for a match of catalyst (chiral phosphine) and reactants.

Table 2. Asymmetric Reductions of Alkyl Phenyl Ketones

Ketone	Hydrosilane	Yield, %	Optical Yield, %
MeCOPh	PhMe ₂ SiH	97	31.6 (S)
<i>t</i> -BuCOPh	PhMe ₂ SiH	84	61.8 (S)
MeCOPh	Me ₃ SiH	100	5.1 (S)
<i>t</i> -BuCOPh	Me ₃ SiH	81	28.1 (S)

Ojima made the most significant contribution in this area when he found a catalyst system which could reduce both alkyl phenyl ketones and dialkyl ketones.^{16f-h} His rhodium(I) complex catalyst with chiral phosphine ligands was prepared *in situ* by the reaction of $[\text{Rh}(1,5\text{-hexadiene})\text{Cl}]_2$ or $[\text{Rh}(1,5\text{-cyclooctadiene})\text{Cl}]_2$ with two equivalents of (-)-(S)- or (+)-(R)-(BMPP) in degassed benzene. Alkyl phenyl ketones were then allowed to react with the monohydrosilane or dihydrosilane in the presence of the chiral rhodium catalyst (0.1-0.5 mole%) in benzene. The resulting optically active silyl ethers were solvolyzed using sodium

methoxide in methanol to afford the corresponding 1-alkyl benzyl alcohols in nearly quantitative yields (Eq. 5). The rate of the reaction is found

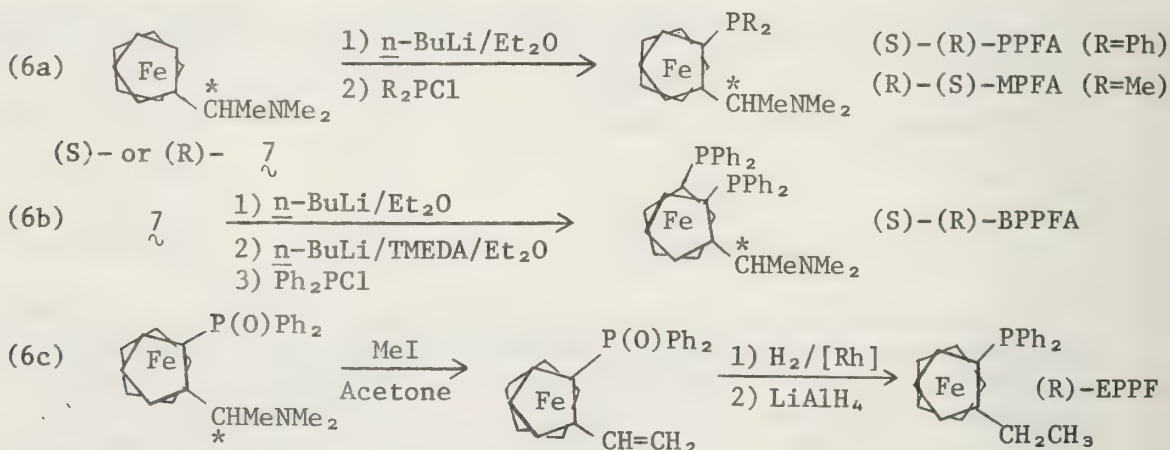


to be slower when a monohydrosilane is employed, and some heating is necessary to complete the reaction (40–50°C). On the other hand, the rate of the reaction increases remarkably when a dihydrosilane is employed (an exothermic reaction occurred at ambient temperature in most cases). Therefore, the reactions of dihydrosilanes with alkyl phenyl ketones were allowed to start at 5–10°C.

In a similar manner, ¹⁶f-h prochiral dialkyl ketones were hydrosilylated using the same chiral rhodium catalyst and converted to the corresponding optically active sec-alcohols in excellent yields.

It should be noted that dialkyl ketones were readily reduced to optically active sec-alcohols without any side reactions in excellent chemical yields and fairly good optical yields. Thus, Ojima's method seems to be the method of choice for the asymmetric reduction of ketones, because it eliminates severe side reactions (the formation of silyl enol ethers) and it extends the method beyond alkyl phenyl ketones into the area of dialkyl ketones with comparable optical yields.

Kumada¹⁶ⁱ has reported a novel chiral phosphine ligand for the catalytic asymmetric hydrosilylation of ketones. These new phosphines have chirality which arises from introducing phosphino groups into α-dimethyl-aminoethylferrocene. The chiral ferrocenylphosphines are readily prepared by way of stereoselective lithiation of (S)-α-ferrocenylethyldimethylamine (⁷) (see Eq. 6a–c) to give (S)-α-[(R)-2-diphenylphosphinoferrocenyl]-ethyldimethylamine (PPFA), (R)-α-[(S)-2-dimethylphosphinoferrocenyl]ethyldimethylamine (MPFA), or (S)-α-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]-ethyldimethylamine (BPPFA). Note that (R)-1-ethyl-2-diphenylphosphinoferrocene (EPPF) has chirality about the iron atom only. Table 3 shows the results of using each of these ligands.



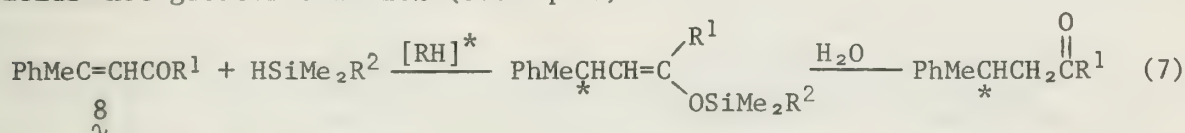
A small amount of work has been done on the heterogeneous asymmetric hydrosilylation of ketones. All of the above methods involve homogeneous catalysis (the catalyst is soluble in the solvent). Heterogeneous catalysis offers the very easy recovery of the very expensive rhodium

Table 3. Asymmetric Hydrosilylations of Ketones Catalyzed by Chiral Ferrocenylphosphine-Rhodium Complexes

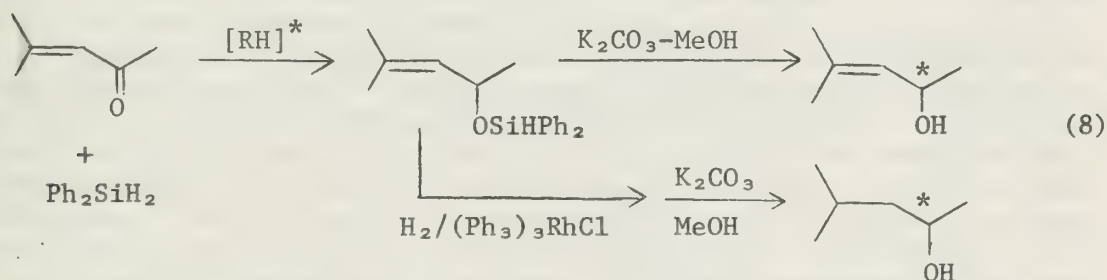
Ketone	Silane	Ligand	Yield, %	Optical Yield, %
EtCOPh	PhMe ₂ SiH	(S)-(R)-PPFA	61	10.5 (R)
EtCOPh	Ph ₂ SiH ₂	(R)-(S)-MPFA	83	38.3 (R)
EtCOPh	Ph ₂ SiH ₂	(S)-(R)-BPPFA	73	24.5 (R)
EtCOPh	Me ₃ SiH	(R)-EPPF	88	5.2 (R)

catalyst. Kagen^{16j} has reported the use of a heterogeneous asymmetric catalyst system, namely a chiral rhodium complex covalently bound to a synthetic insoluble support (a Merrifield resin).¹⁷ In general, the optical yields for these catalyst systems are only slightly lower than for the homogeneous systems, however, much more work remains to be done on the effect the support has on the reduction mechanism.

Asymmetric Reductions of α,β -Unsaturated Ketones. The selective asymmetric reduction of α,β -unsaturated ketones has been investigated by Kumada^{18a} and Ojima.^{18b} Initially Sadykh-Zade and Petrov reported that chloroplatinic acid-catalyzed hydrosilylation of α,β -unsaturated carbonyl compounds takes place in a 1,4 fashion.¹⁹ Ojima found, however, that highly selective 1,2- as well as 1,4-addition of hydrosilanes to α,β -unsaturated terpene ketones can be achieved by using $(\text{Ph}_3\text{P})_3\text{RhCl}$, the selectivity depending markedly on the nature of the hydrosilane employed. For example, the reaction using mono-hydrosilanes was found to proceed in a manner of 1,4-addition, while di-hydrosilanes undergo 1,2-addition to carbonyl functionalities with little exception.^{9d} Thus, Kumada^{18a} showed that asymmetric hydrosilylation of α,β -unsaturated carbonyl compounds using $[\text{Rh}[(\text{R})-(\text{PhCH}_2)\text{MePhP}]_2\text{H}_2\text{S}_2]^+$ (S=solvent) can be carried out exclusively in a 1,4 fashion at room temperature, however, with optical yields not greater than 16% (see Eq. 7).

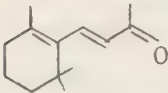
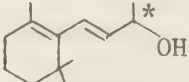
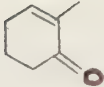
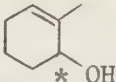


Ojima^{18b} then showed that the asymmetric hydrosilylation of α,β -unsaturated carbonyl compounds using $[(\text{R})\text{-BMPP}]_2\text{Rh}(\text{S})\text{Cl}$ (S = solvent) can be carried out in a 1,2 fashion under very mild conditions (temperatures below 25°C) and in moderately high optical yields as determined by nmr using Eu(facam)₃ (see Eq. 8). Note the versatility of the reaction in

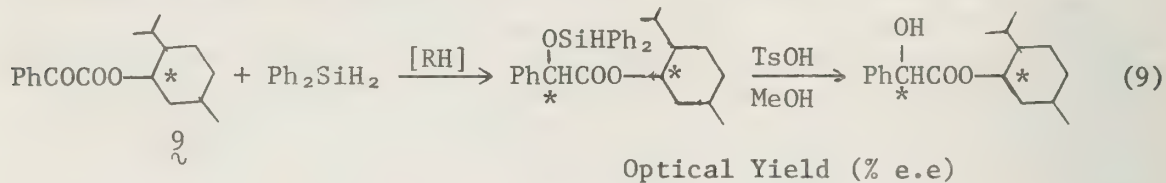


Eq. 8 as the olefinic double bond can be reduced separately by hydrogenation. Table 4 shows two examples of the usefulness of this reaction.

Table 4. Selective Asymmetric Reduction of α,β -Unsaturated Ketones Using Catalytic Hydrosilylation

Ketone	Hydrosilane	Chiral Ligand	Product	Optical Yield, %
	α -NpPhSiH ₂	(+)-BMPP		33.5
	α -NpShSiH ₂	(+)-BMPP		43

Double Asymmetric Reductions. Conceptually, there are several distinct ways in which the asymmetric reduction of an α -keto ester to give the corresponding optically active α -hydroxy ester can be achieved: (a) by the reduction of a chiral ester with an achiral reducing agent; (b) by the reduction of an achiral ester with a chiral reducing agent; and (c) by a combination of chiral ester and chiral reducing agent. Ojima²⁰ was able to test these methods when he performed catalytic asymmetric reductions of benzoylformates in the following ways: (a) a simple asymmetric reduction of (-)-menthyl benzoylformate (**9**) by hydrosilylation catalyzed by a rhodium complex with achiral phosphine ligands, (Ph₃P)₃RhCl; (b) double asymmetric reduction of **9** using a rhodium complex with a chiral phosphine ligand ((-)-DIOP); and (c) double asymmetric reduction of **9** using a rhodium complex with (+)-DIOP as chiral ligand (see Eq. 9).



	Optical Yield (% e.e)
(a) Rh = (Ph ₃ P) ₃ RhCl	32 (S)
(b) Rh = [(-)-DIOP]Rh(S)Cl	21 (R)
(c) Rh = [(+)-DIOP]Rh(S)Cl	60 (S)

(S = solvent)

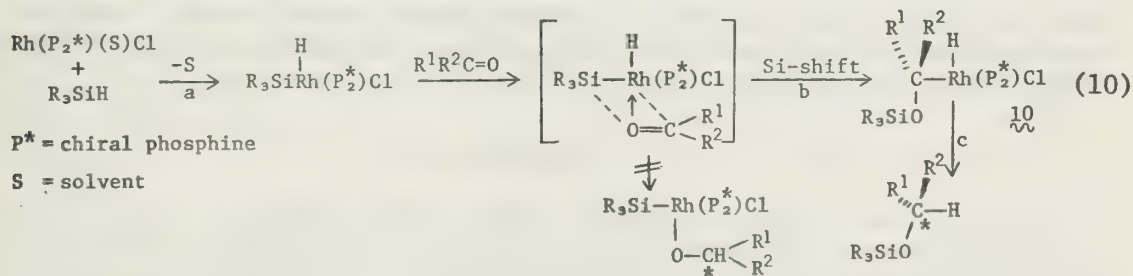
Experiment (a) estimates the influence of the (-)-menthyl group on the induction of asymmetry. Experiment (b) shows that the opposing double asymmetric induction by the chiral catalyst and the (-)-menthyl group affords (R)-(+)-mandelate with rather low stereoselectivity. The rhodium catalyst with (-)-DIOP as a chiral ligand is found to favor the production of (R)-mandelate in this system, and the direction of asymmetric induction is opposite to that by the (-)-menthyl group. The production of (R)-mandelate is favored in the case of the asymmetric reduction of ethyl benzoylformate with the use of [(-)-DIOP]Rh(S)Cl and Ph₂SiH₂ in which the optical yield is extremely low (1.4% e.e.) despite the absence of the negative effect of the (-)-menthyl group. These results clearly indicate that the bulkiness of the ester group is an essential factor for determining the effectiveness and the direction of the asymmetric induction. Experiment (c) demonstrates the effective double asymmetric induction reaction. In this case, the direction of asymmetric induction by [(+)-DIOP]Rh(S)Cl is well matched to the effect of the (-)-menthyl group.

The effect of the (-)-menthyl group can be shown by examining the reaction of Eq. 9 when catalyzed by a rhodium complex and the same reaction catalyzed with LAH-cyclohexanol. The hydrosilylation with the rhodium complex shows an opposite influence on determining the direction of the asymmetric reduction compared with the LAH-cyclohexanol reduction.²⁰ Namely, the former favored the formation of (S)-mandelate, while the latter favored (R)-mandelate. The latter case can be well understood by Prelog's generalization²¹ in which the two carbonyl groups of the α -keto ester are in the anti-coplanar conformation.

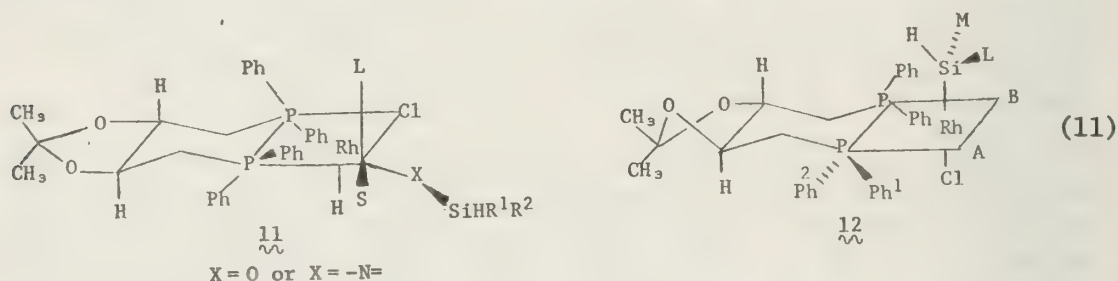
According to Prelog's stereochemical considerations, the two carbonyl groups of **9** should be in the syn-coplanar conformation for the former case. However, it has previously been shown that the stereochemical course of the hydrosilylation catalyzed by a rhodium complex follows a product development control²² rather than a steric approach control,²² and that the reaction proceeds via a silyloxyalkyl rhodium complex.^{16b,e,g,h} Consequently, the former results may be best explained by postulating a template effect of the silyl group by chelation which arises from the coordination of the remaining carbonyl to the silyl group.²³

Mechanism. A mechanism for the asymmetric reduction of unsaturated molecules via hydrosilylation should take into account the nature of the hydrosilane used and the bulkiness of the incoming unsaturated organic molecule in order to fully explain the observed results. Ojima has proposed a mechanism to account for the induction of asymmetry when the BMPP-rhodium(I) complex catalyst is used.^{16f,h} He previously reported^{16b} the intermediacy of the α -silyloxyalkylrhodium complex in the hydrosilylation of terpene ketones catalyzed by $(\text{Ph}_3\text{P})_3\text{RhCl}$. Therefore, it seems probable that the intermediate α -silyloxyalkylrhodium complex would also play a key role in the asymmetric reduction of unsaturated molecules. Thus, Ojima's proposed mechanism involves the steps shown in Eq. 10. Of the steps involved, b must play the most important role in inducing asymmetry at the carbonyl carbon because this step determines a predominant configuration and the extent of enantiomeric excess of the product.

Intermediate **10** can take one of three configurations depending on the steric bulk of each ligand. Thus, using this mechanism, Ojima found that the configurations of the resulting alcohols are consistently predicted when the bulkiness of the silyloxy groups are estimated as follows: $\text{c-Hex} > \text{t-Bu} > \text{PhMe}_2\text{SiO} > \text{Ph} > \text{EtMe}_2\text{SiO} > \text{Et}_2\text{HSiO} > \text{i-Pr} > \text{Ph}_2\text{HSiO} > \text{PhMeHSiO} > \text{Et} > \text{Me}$.^{16f} It should also be noted that this mechanism can also be successfully applied to the reaction of α -, β - and γ -keto esters, where certain electronic attractive interactions between the ester group and the central rhodium atom is taken into account.¹³



The steric requirements in the coordination sphere of the DIOP-rhodium complex are quite different from those of the BMPP-rhodium complex; nevertheless, the intermediate α -silyloxyalkyl-rhodium complex 10 may also play a key role for the induction of asymmetry. The proposed model works quite well for the prediction of the preferred configuration in the case of simple alkyl phenyl ketones or Schiff bases by postulating the most favorable structure of the intermediate complex 10 as in 11. In these cases, the silyloxy (or silylamino) moiety is the bulkiest substituent in the coordination sphere on the (+)-DIOP-rhodium complex and should occupy the least hindered quasi-equatorial position based on the inspection of Dreiding models.¹³ It should be noted that this mechanism also predicts the products quite well in the case of keto esters, where the ester group takes a quasi-apical position, the methyl occupies the most congested site, and the bulkier silyloxy group occupies the least hindered site.



Glaser has also proposed a mechanism for the induction of asymmetry in asymmetric hydrogenation and hydrosilylation reactions using intermediate complex 12.²⁴ Although Glaser can predict the results of asymmetric hydrosilylations with his mechanism, it does seem to have some disadvantages that Ojima's does not possess. Glaser proposes a mechanism of steric approach control²² for hydrosilylations in analogy to hydrogenations; however, it has been shown that the mechanisms of these reactions are quite different when carbonyl compounds are employed as substrates in hydrosilylation reactions,^{16f} (the hydrogenation mechanism with an alkoxyrhodium complex intermediate cannot account for the observed changes in optical yields on changing the silane structure) and it is strongly suggested that product development control²² is operative for the formation of complex 10 in hydrosilylations.¹³ Secondly, Glaser puts the silyl moiety in the upper apical position which is more sterically hindered than sites A or B or the lower apical position (occupied by the chlorine). Finally, he proposes that the coordination site B is less hindered than site A; however, the steric hindrance caused by Ph^1 seems to be estimated to be too high in his inspection. Ojima's model¹³ assumes that the conformation of 11 corresponds exactly to the most preferable one of possible conformations according to Dreiding models, and generally accounts for product formation better than Glaser's model. Ojima's mechanism also works well when a cationic rhodium complex may be involved instead of a neutral species.^{13,16f}

BIBLIOGRAPHY

1. H. O. House, "Modern Synthetic Reactions", second ed., W. A. Benjamin, Menlo Park, California, 1972, chapt. 1-4 and references therein.
2. I. Ojima, Organotransition-Met. Chem., Proc. Jap.-Am. Semin. 1st 1974, Y. Ishii and M. Tsutsui, Ed., published 1975, p. 255.
3. See the following references for the first reports of the addition of organosilicon hydrides to unsaturated bonds: (a) L. H. Sommer, E. W.

- Pietrusza, and F. C. Whitmore, J. Am. Chem. Soc., 69, 188 (1947); (b) H. C. Miller and R. S. Schreiber, U. S. Patent 2,379,821 (1945); (c) A. J. Barry and D. E. Hook, U. S. Patent 2,626,271 (1953); (d) G. H. Wagner and C. O. Strother, U. S. Patent 2,632,013 (1953); (e) C. A. McKenzie, L. Spialter, and M. Schoffman, French Patent 961,878 (1949).
4. I. Ojima and M. Nihonyanagi, J. Chem. Soc. Chem. Commun., 938 (1972).
5. I. Ojima, T. Kogure, and Y. Nagai, Tetrahedron Lett., 2475 (1973).
6. For an example see: J. F. Klebe, J. B. Bush, Jr., and J. E. Lyons, J. Am. Chem. Soc., 86, 4400 (1964).
7. I. Ojima, S. Inaba, and Y. Nagai, Tetrahedron Lett., 4363 (1973).
8. I. Ojima and S. Inaba, J. Organometal. Chem., 72, C11 (1974).
9. (a) I. Ojima, M. Kumagai, and Y. Nagai, J. Organometal. Chem., 111, 43 (1976); (b) I. Ojima, *ibid.*, 134, C1 (1977); (c) I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi, K. Nakatsugawa, and Y. Nagai, *ibid.*, 94, 449 (1975); (d) I. Ojima, T. Kogure, and Y. Nagai, Tetrahedron Lett., 5035 (1972); (e) I. Ojima, T. Kogure, M. Nihonyanagi, H. Kona, S. Inaba, and Y. Nagai, Chem. Lett., 501 (1973).
10. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice Hall, 1971, sections 2 and 5 and references therein.
11. G. Vavon and A. Antonini, C. R. Acad. Sci., 230, 1870 (1950); 232, 1120 (1951).
12. H. Horeau, H. B. Kagan, and J. P. Vigneron, Bull. Soc. Chim. Fr., 3795 (1968).
13. I. Ojima, T. Kogure, and M. Kumagai, J. Org. Chem., 42, 1671 (1977); see also I. Ojima, T. Kogure, and Y. Nagai, Tetrahedron Lett., 1889 (1974).
14. H. B. Kagan and T. P. Dang, J. Am. Chem. Soc., 94, 6429 (1972).
15. A. I. Meyers and D. E. Mihelich, J. Org. Chem., 40, 1186 (1975).
16. (a) K. Yamamoto, T. Hayashi, and M. Kumada, J. Organometal. Chem., 46, C65 (1972); (b) I. Ojima, M. Nihonyanagi, and Y. Nagai, Bull. Chem. Soc. Jap., 45, 3722 (1972); (c) I. Ojima, T. Kogure, M. Nihonyanagi, and Y. Nagai, *ibid.*, 45, 3506 (1972); (d) P. Bonvicini, A. Levi, G. Modena, and G. Scorrano, J. Chem. Soc. Chem. Commun., 1188 (1972); (e) K. Yamamoto, T. Hayashi, and M. Kumada, J. Organometal. Chem., 54, C45 (1973); (f) I. Ojima, T. Kogure, M. Kumagai, S. Horiuchi, and T. Sato, *ibid.*, 122, 83 (1976); (g) I. Ojima, T. Kogure, and Y. Nagai, Chem. Lett., 541 (1973); (h) I. Ojima and Y. Nagai, *ibid.*, 223 (1974); (i) T. Hayashi, K. Yamamoto, and M. Kumada, Tetrahedron Lett., 4405 (1974); (j) W. Dumont, J.-C. Poulin, T.-P. Dang, and H. B. Kagan, J. Am. Chem. Soc., 95, 8295 (1973).
17. R. B. Merrifield, J. Am. Chem. Soc., 85, 2149 (1963); 86, 304 (1964).
18. (a) T. Hayashi, K. Yamamoto, and M. Kumada, Tetrahedron Lett., 3 (1975); (b) I. Ojima, T. Kogure, and Y. Nagai, Chem. Lett., 985 (1975).
19. S. I. Sadykh-Zade and A. D. Petrov, Zh. Obshch. Khim., 29, 3194 (1959).
20. I. Ojima and Y. Nagai, Chem. Lett., 191 (1975).
21. V. Prelog, Helv. Chim. Acta., 36, 308 (1953).
22. W. G. Dauben, G. J. Fonken, and D. S. Noyce, J. Am. Chem. Soc., 78, 2579 (1956).
23. S. K. Dhar, V. Doron, and S. Kirschner, J. Am. Chem. Soc., 80, 753 (1958).
24. R. Glaser, Tetrahedron Lett., 2127 (1975).
25. For further lead references see: (a) R. J. P. Corriu and J. J. E. Moreau, J. Organometal. Chem., 85, 19 (1975); (b) R. J. P. Corriu and J. J. E. Moreau, *ibid.*, 64, C51 (1974); (c) I. Ojima and M. Kumagai, *ibid.*, 66, C14 (1974); (d) S. Washburn, *ibid.*, 123, 1 (1976); (e) L. Hgedus, *ibid.*, 126, 151 (1977); (f) L. H. Sommer, "Stereochemistry, Mechanism and Silicon", McGraw-Hill Inc., New York, N.Y., 1965.

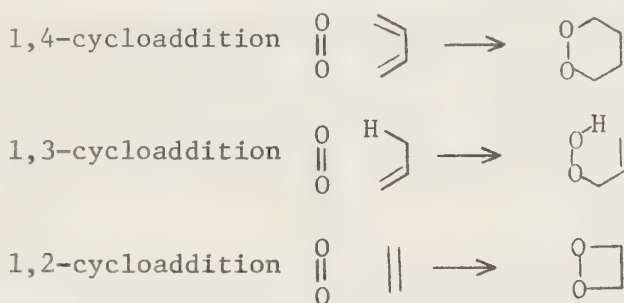
THE REACTION OF SINGLET MOLECULAR OXYGEN WITH ALKENES

Reported by Steven P. Schmidt

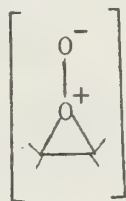
November 17, 1977

Only in the past fifteen years has it been firmly established that electronically excited singlet molecular oxygen ($^1\Delta_g$) is the critical reactive intermediate in dye-sensitized photooxygenations, as well as in oxygenations brought about by the hydrogen peroxide-hypochlorite system and by microwave discharge.¹⁻⁴ As a result, a vigorous research on the chemistry of this intriguing intermediate, including in particular its reaction with a wide variety of organic substrates, was initiated.

Three modes of reaction of the $^1\Delta_g$ state of oxygen with alkenes have been observed:^{1,5,6} 1,4-cycloaddition with conjugated dienes leading to endoperoxides, 1,3-cycloaddition ("ene" type reaction) with olefins which possess allylic hydrogens affording allylic hydroperoxides, and 1,2-cycloaddition yielding dioxetanes, which subsequently cleave to carbonyl products.



The synthetic value of these three reactions, as simple yet elegant methods of introducing the peroxide linkage into organic substrates, has been well documented with an overwhelming wealth of examples of each.⁷⁻⁹ The mechanisms of these reactions, however, with the exception of the 1,4-cycloaddition which has been accepted as proceeding via a 6-membered concerted transition state,¹⁰ remain the subject of much heated controversy. Specifically, attention has been focused on the possibility of a peroxirane intermediate or a peroxirane-like transition state.

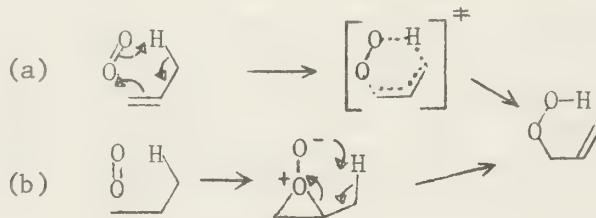


1,3-Cycloaddition. The reaction of singlet oxygen with alkyl-substituted olefins to give allylic hydroperoxides is the most extensively studied of these photosensitized oxygenations. Much of the earlier work has been reviewed^{1,5,11} and hence will be only briefly summarized here.

Partly due to the nature of the reaction and partly due to the ambiguity of experimental results, the mechanism of the 1,3-cycloaddition reaction has not been firmly established, despite extensive investigation. Of the several possibilities,⁶ the two mechanisms which remain in debate are the concerted 6-center process (Scheme Ia), first proposed by Nickon,¹² and the peroxirane mechanism (Scheme Ib) introduced by Sharp.¹³ While both mechanisms are cis-cyclic processes, as required by stereochemical

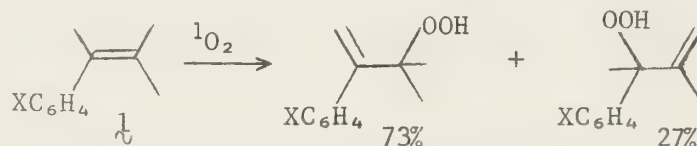
findings,¹⁴ the details focus on whether C-O formation and C-H cleavage are concurrent or sequential. Electronic, steric, conformation, solvent, and isotope effects have been investigated, none of which, however, provide conclusive evidence in favor of either mechanism.

Scheme I



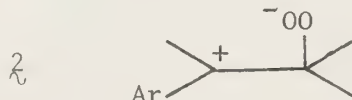
Singlet oxygen is mildly electrophilic, and the 1,3-cycloaddition reaction is therefore sensitive to the nucleophilicity of the olefinic bond.¹⁵ The excellent correlation between the rate of peracid oxidation of variously substituted olefins, and the rate of their reaction with singlet oxygen, was used by Kopecky to support the intermediacy of a peroxirane.¹⁵

Foote¹⁶ examined electronic effects more fully by determining relative reaction rates for a series of aryl substituted 2-methyl-3-phenyl-2-butenes ($\mathbf{1}$). The observed correlation of rates with σ (suggesting a lack



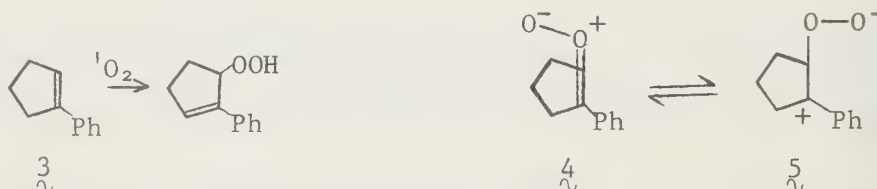
X = p-CH₃O, p-CH₃, p-Cl, p-CN

of direct resonance interaction) and the interesting result that product distribution is independent of substituent, argue against localized charge, as in $\mathbf{2}$. A similar lack of a strong Markovnikov directing influence has



been observed with trialkyl olefins, which afford approximately equal amounts of secondary and tertiary hydroperoxides.^{1,5} Most authors have interpreted these results in terms of the concerted mechanism, but by no means are they inconsistent with a closed peroxirane intermediate.⁶

In contrast, Jefford's recent report of a dominant Markovnikov effect in the photooxygenation of 2-phenyl cycloalkenes ($\mathbf{3}$),¹⁷ is suggestive of the intermediacy of peroxirane $\mathbf{4}$ or zwitterion $\mathbf{5}$. The regioselective



addition of singlet oxygen to 1-alkyl-2,2-dicyclopropyl-ethylene derivatives¹⁸ also favors a peroxirane intermediate.

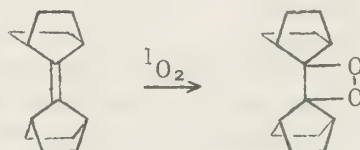
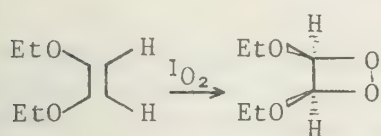
The solvent effect on the 1,3-cycloaddition reaction has been studied by Foote.¹⁹ Including a correction for the variation of singlet oxygen

lifetime,²⁰ only a four-fold variation of photooxygenation reaction rate was observed for a series of solvents ranging from carbon disulfide to methanol. This lack of a strong solvent effect has been used to argue against the intermediacy of a polar species. Theoretical calculations,^{22,23} however, as well as other evidence,²⁴ suggest the transition state leading to peroxirane is reactant-like, and hence involves only minor charge separation.

The intra- and intermolecular primary deuterium isotope effects for the 1,3-cycloaddition reaction are in the range of 1.1-2.0.^{25,26} Clearly, this is consistent with rate-determining formation of a peroxirane intermediate but, at the same time, is not in conflict with a concerted mechanism in which C-H bond cleavage is minimal at the transition state.²⁷

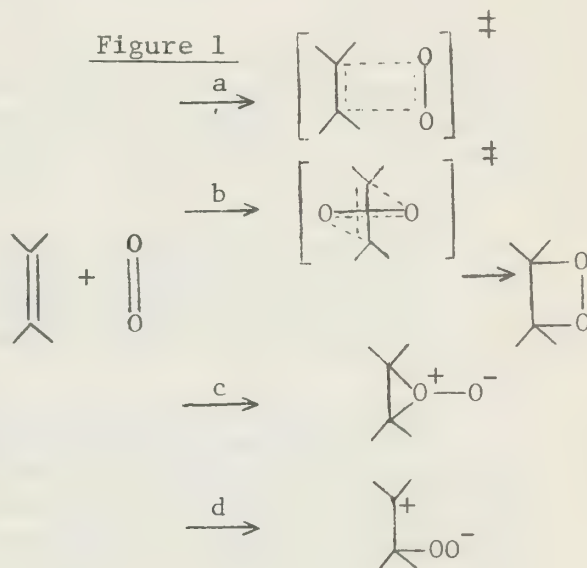
Thus, an experimental distinction between the concerted and the peroxirane mechanisms for the 1,3-cycloaddition reaction is difficult to make. MINDO/3 calculations²³ favor the peroxirane intermediate, but in view of the futility of attempts at direct detection²⁸ and the lack of substantiated chemical traps^{25,29,30} of a peroxirane intermediate, a solution to this mechanistic ambiguity is not evident.

1,2-Cycloaddition. Singlet oxygen reacts with electron rich olefins and with alkenes which have hindrance to the ene-reaction to yield di-oxetanes by a stereospecific cis^{31,32} 1,2-cycloaddition.³³



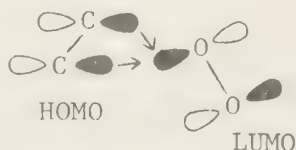
The apparent concertedness of singlet oxygen's 1,2-cycloaddition, and the consequent unique position of this electrophilic reagent in terms of orbital symmetries, have stimulated much interest in and discussion of the mechanism of this reaction. Four possible modes (Fig. 1) for the 1,2-cycloaddition have been considered theoretically at several levels.

State correlation diagrams^{6,34} and orbital phase continuity arguments³⁵ suggest that the $(\pi_s^2 + \pi_s^2)$ approach (Fig. 1a) is forbidden, although it has been proposed⁶ to be allowed for alkenes with low ionization potentials. The concerted $(\pi_s^2 + \pi_a^2)$ approach (Fig. 1b) is symmetry allowed^{6,23} and has been considered a likely path for dioxetane formation. Peroxirane formation (Fig. 1c) has likewise been shown, on the basis of correlation diagrams⁶ and a consideration of frontier orbital interaction³⁶ to be an allowed process. Zwitterionic intermediates (Fig. 1d) have been considered in the case of electron rich olefins, especially those with polarized double bonds.



Fukui,³⁶ by means of a HOMO-LUMO overlap analysis, pointed out that the initial orbital interaction is most effective at the nuclear arrangement of Figure 2. Investigation by semiempirical SCF-CNDO/2 calculations

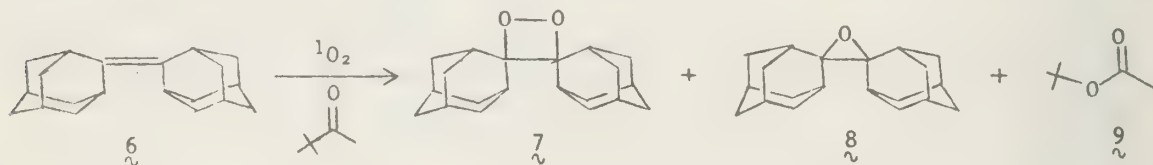
Figure 2



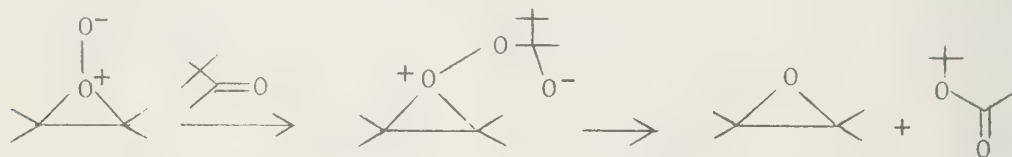
of the potential energy surface for the transformation of this initially formed peroxirane into dioxetane, which indicated only a shallow energy minimum to be present, prompted Fukui to designate the peroxirane structure a "quasi" intermediate.³⁷

According to MINDO/3 calculations by Dewar,²³ the 1,2-cycloaddition of $1O_2$ and ethylene passes through a peroxirane intermediate which subsequently rearranges to dioxetane. In contrast, recent *ab initio* studies (GVB-CI) by Harding and Goddard³⁸ place unsubstituted peroxirane 53 kcal above dioxetane and 16 kcal above reactants. Activation parameters were not calculated, but Harding and Goddard anticipate a sizeable barrier to peroxirane formation due to an extensive change in orbital character in proceeding from reactants to peroxirane.

Schaap had seemingly provided the first direct evidence for a peroxirane intermediate in reporting that the dye-sensitized photooxygenation of biadamantylidene (6) in pinacolone gave the corresponding dioxetane (7) and oxirane (8), with concomitant formation of *t*-butylacetate (9).³⁹

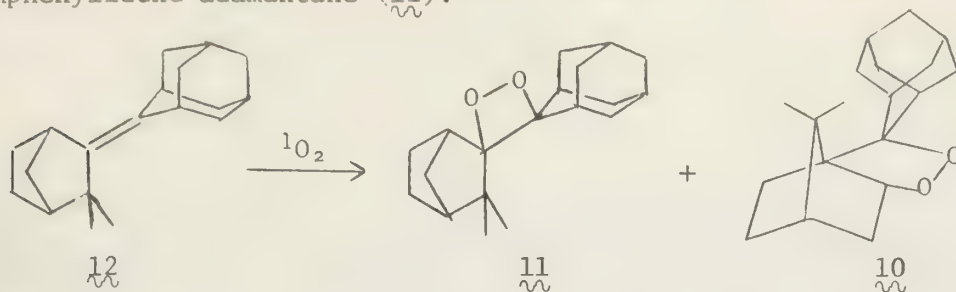


Steric strictures in the adamantane skeleton were thought to inhibit rearrangement and hence to preserve the life of the peroxirane to the extent of allowing it to react in a Baeyer-Villiger fashion with pinacolone to give oxirane and *t*-butyl acetate (9).

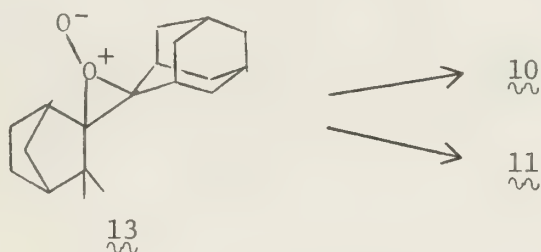


Subsequent investigations, however, demonstrated that similar alkenes, including binorbornylidene⁴⁰ and norbornene,⁴⁸ afforded oxiranes in addition to dioxetanes upon photooxygenation in inert solvents, as well as in pinacolone. Jefford therefore re-examined the photooxygenation of biadamantylidene (6) in pinacolone and, in contrast to Schaap's report,³⁹ uncovered no trace of *t*-butyl acetate.⁴² Significantly, Jefford also discovered the dioxetane-oxirane product ratio to be strongly dependent on the sensitizer. The mechanism for oxirane formation has not been firmly established, although several possibilities have been proposed.^{42,43}

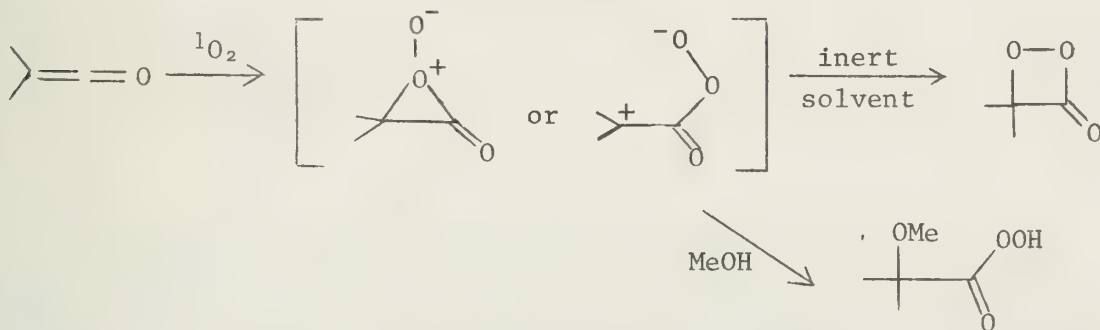
McCapra has quite recently reported the isolation of 1,2-dioxolanes (10), along with the expected dioxetane 11, from the reaction of $^1\text{O}_2$ with camphenylidene-adamantane (12).⁴⁴



This finding is suggestive of the intermediacy of a peroxirane (13), or closely related species with strong carbonium ion character, which partitions between dioxolane and dioxetane.

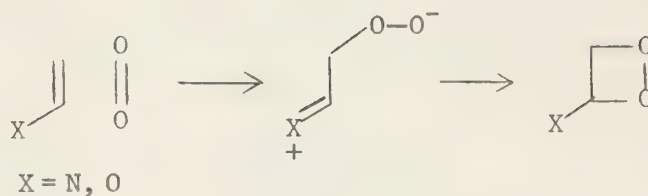


Recently, Turro has provided evidence for a peroxirane or zwitterionic intermediate in the reaction of singlet oxygen with ketenes.⁴⁵ In inert solvents, reaction leads to α -peroxylactones. In methanol, however, α -peroxylactone formation is completely suppressed, and α -methoxyperacetic acids are produced, presumably via proton abstraction by an initially formed ionic intermediate.

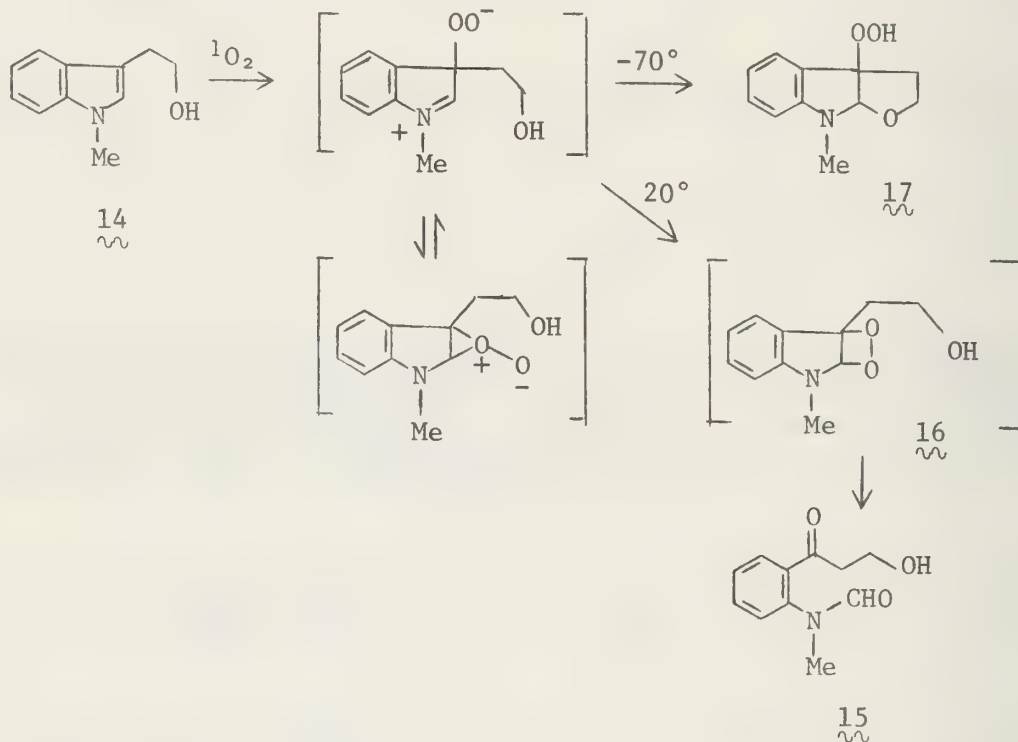


Solvent polarity criteria on product distribution (1,2- vs. 1,3-cycloaddition) have been investigated for several systems. In three cases, increasing solvent polarity reportedly favors the 1,2- over the 1,3-cycloaddition mode,⁴⁶ but conflicting results have also appeared.⁴⁷

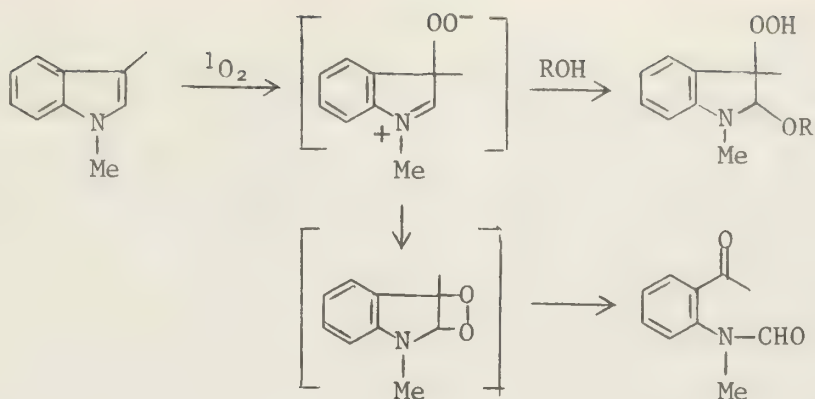
Cycloadditions with Polarized Olefinic Bonds. Enol ethers and tertiary enamines undergo a 1,2-cycloaddition with singlet oxygen, affording dioxetanes, which subsequently cleave to carbonyl, ester, or amide fragments.^{31,48} For an electron-rich, polarized π bond, the 1,2-cycloaddition has been considered as potentially proceeding through an initially formed zwitterionic intermediate which may then undergo facile rearrangement to dioxetane.^{25,35,37}



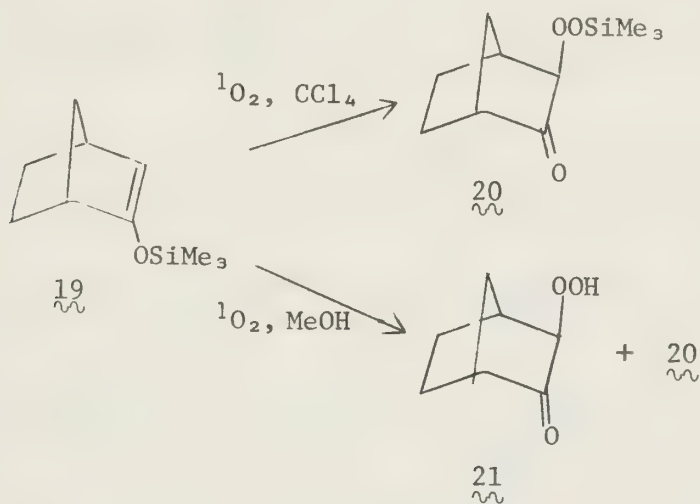
Recent investigations of the sensitized photooxygenations of N-methylindole derivatives provide evidence that, at least for these cases, a polar peroxide is indeed the initial intermediate.⁴⁹ Photooxygenation of N-methyl-tryptophol (14) at room temperature leads to the ring cleavage product 15, presumably via dioxetane 16. However, photooxygenation at -70° leads exclusively to hydroperoxide 17.⁵⁰ Photooxygenation of N^b-methoxycarbonyl-N^a-methyltryptamine results in an analogous reaction.⁵¹



Additionally, the polar peroxide intermediate resulting from the low temperature photooxygenation of 1,3-dimethylindole (18) was trapped intermolecularly by alcohols.⁵² Again, the product ratio is highly temperature sensitive, the alcohol addition reaction predominating at low temperatures, and the ring cleavage predominating at ambient temperatures.



Jefford⁵³ has recently implicated a polar peroxy intermediate in the photooxygenation of silyl enol ether 19. In aprotic solvents, silyl peroxy ketone 20 is the exclusive product, while in methanol, hydroperoxy ketone 21 is observed in addition to 20. As 20 is stable under reaction conditions, 21 most likely arises via proton abstraction by an initially formed zwitterionic intermediate or its peroxirane tautomer.



Conclusions. Recent investigations point to the involvement of peroxidic intermediates in the reaction of singlet oxygen with electron rich, polarized double bonds. It is apparent, however, that for reaction with non-polarized olefins, both in the 1,2- and the 1,3-cycloaddition modes, the indirect experimental evidence generated thus far does not allow a firm conclusion as to the involvement of peroxirane intermediates. A solution to this intriguing mechanistic problem awaits further experimentation.

BIBLIOGRAPHY

1. C. S. Foote, *Acc. Chem. Res.*, 1, 104 (1968).
2. (a) H. Kautsky and H. de Bruijn, *Naturwiss.*, 19, 1043 (1931); (b) H. Kautsky, *Trans. Farad. Soc.*, 35, 216 (1939).
3. C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, 86, 3879 (1964).
4. E. J. Corey and W. C. Taylor, *J. Am. Chem. Soc.*, 86, 3881 (1964).
5. K. Gollnick, *Advan. Photochem.*, 6, 1 (1968).
6. D. R. Kearns, *Chem. Rev.*, 71, 395 (1971).
7. G. Ohloff, *Pure Appl. Chem.*, 43, 481 (1975).
8. W. Adam, *Chem. Ztg.*, 99, 142 (1975).
9. D. W. Denny and A. Nickon, *Org. React.*, 20, 133 (1973).
10. (a) K. Gollnick and G. O. Schenck in J. Hamer (Ed.): *1,4-Cycloaddition Reactions*, Academic Press, Inc., New York, N.Y., 1967; M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 99, 2239 (1977).
11. C. S. Foote, *Pure Appl. Chem.*, 27, 635 (1971).
12. A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, 81, 6330 (1959).
13. D. B. Sharp, *Abstr. 130th A.C.S. Meeting*, New York, N.Y., Sept. 1960, p. 79.
14. C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Lett.*, 4111 (1965).
15. K. R. Kopecky and H. J. Reich, *Can. J. Chem.*, 43, 2265 (1965).
16. C. S. Foote and R. W. Denny, *J. Am. Chem. Soc.*, 93, 5162 (1971).
17. C. W. Jefford and C. G. Rimbault, *Tetrahedron Lett.*, 2479 (1976).
18. G. Rousseau, P. Le Perchec, and J. M. Conia, *Tetrahedron Lett.*, 45 (1977).
19. C. S. Foote and R. W. Denny, *J. Am. Chem. Soc.*, 93, 5168 (1971).
20. R. D. Ashford and E. A. Ogryzlo, *J. Am. Chem. Soc.*, 97, 3604 (1975).
21. P. B. Merkel and D. R. Kearns, *J. Am. Chem. Soc.*, 94, 7244 (1972).
22. D. R. Kearns, W. Fenical, and P. Radlick, *Ann. N. Y. Acad. Sci.*, 171, 32 (1970).
23. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 97, 3978 (1975).
24. C. W. Jefford, M. H. Laffer, and A. F. Boschong, *J. Am. Chem. Soc.*, 94, 8904 (1972).
25. K. R. Kopecky and J. H. van der Sande, *Can. J. Chem.*, 50, 4034 (1972).
26. A. Nickon, V. T. Chuang, P. J. L. Daniels, R. W. Denny, J. B. DiGiorgio, J. Tsunetsuga, H. G. Vilhuber, and E. Werstink, *J. Am. Chem. Soc.*, 94, 5517 (1972).
27. C. W. Jefford and A. F. Boschong, *Helv. Chim. Acta*, 57, 2242 (1974).
28. J. C. Carmier and X. Deglise, *Bull. Soc. Chim. Fr.*, 868 (1973).
29. W. Fenical, D. R. Kearns, and P. Radlick, *J. Am. Chem. Soc.*, 91, 7771 (1969).
30. (a) K. Gollnick, D. Haisch, and G. Schade, *J. Am. Chem. Soc.*, 94, 1747 (1972); (b) C. S. Foote, T. T. Fujimoto, and Y. C. Chang, *Tetrahedron Lett.*, 45 (1972).
31. P. D. Bartlett and A. P. Schaap, *J. Am. Chem. Soc.*, 92, 3223 (1970).
32. A. P. Schaap and N. Tontopanish, *J. Chem. Soc. Chem. Commun.*, 490 (1972).
33. P. D. Bartlett, *Chem. Soc. Rev.*, 5, 149 (1976).
34. D. R. Kearns, *J. Am. Chem. Soc.*, 91, 6554 (1969).
35. K. Yamagochi, T. Fueno, and H. Fakutome, *Chem. Phys. Lett.*, 22, 466 (1973).
36. S. Inagaki, S. Yamabe, H. Fujimoto, and K. Fukui, *Bull. Chem. Soc. Jap.*, 45, 3510 (1972).
37. S. Inagaki and K. Fukui, *J. Am. Chem. Soc.*, 97, 7480 (1975).
38. L. B. Harding and W. A. Goddard, III, *J. Am. Chem. Soc.*, 99, 4520 (1977).
39. A. P. Schapp and G. R. Faler, *J. Am. Chem. Soc.*, 95, 3381 (1973).

40. P. D. Bartlett and M. S. Ho, *J. Am. Chem. Soc.*, 96, 627 (1974).
41. C. W. Jefford and A. F. Boschung, *Helv. Chim. Acta*, 57, 2257 (1974).
42. C. W. Jefford and A. F. Boschung, *Tetrahedron Lett.*, 4771 (1976).
43. M. J. S. Dewar, A. C. Griffin, W. Thiel, and I. J. Turchi, *J. Am. Chem. Soc.*, 97, 4439 (1975).
44. F. McCapra and I. Beheshti, *J. Chem. Soc. Chem. Commun.*, 517 (1977).
45. N. J. Turro, Y. Ito, M.-F. Chow, W. Adam, O. Rodriguez, and F. Yang, *J. Am. Chem. Soc.*, 99, 5836 (1977).
46. (a) P. D. Bartlett, G. P. Mendenhall, and A. P. Schaap, *Ann. N. Y. Acad. Sci.*, 171, 79 (1970); (b) N. M. Hasty and D. R. Kearns, *J. Am. Chem. Soc.*, 95, 3379 (1973); (c) W. Ando, K. Watanabe, J. Sazuki, and T. Migita, *J. Am. Chem. Soc.*, 96, 6766 (1974).
47. A. G. Schultz and R. H. Schlessinger, *Tetrahedron Lett.*, 2731 (1970).
48. C. S. Foote, A. A. Dzakpasa, and J. W.-P. Lin, *Tetrahedron Lett.*, 1247 (1975).
49. I. Saito, T. Matsuura, M. Nakagawa, and T. Hino, *Acc. Chem. Res.*, 10, 346 (1977).
50. I. Saito, M. Imuta, S. Matsugo, and T. Matsuura, *J. Am. Chem. Soc.*, 97, 7191 (1975).
51. M. Nakagawa, H. Okajima, and T. Hino, *J. Am. Chem. Soc.*, 99, 4424 (1977).
52. I. Saito, M. Imuta, Y. Takahashi, S. Matsugo, and T. Matsuura, *J. Am. Chem. Soc.*, 99, 2005 (1977).
53. C. W. Jefford and C. C. Rimbault, *Tetrahedron Lett.*, 2375 (1977).

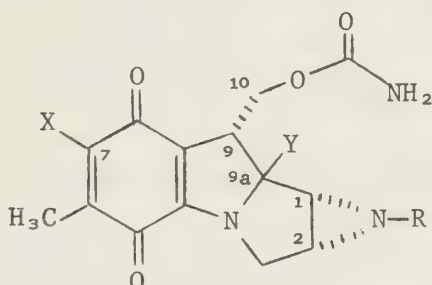
THE MITOMYCINS: ARE THEY "JUST ANOTHER NATURAL PRODUCT"?

Reported by Charles Hutchins

November 21, 1977

In 1956 two crystalline compounds were isolated from the broth of cultures of *Streptomyces caespitosus* by Hata et al.¹ which demonstrated strong antitumor and antibacterial activity. Since these were only two of many compounds in the broth, the antibiotics were designated mitomycin A and B. Soon three related compounds of the mitomycin family were isolated from other *Streptomyces* species.^{2,3,4} In 1962, structures for the mitomycins were proposed based on spectrometric data of the acid-hydrolysis products.⁵ Concurrently, X-ray structure determination⁶ agreed with the proposed structures and showed the stereochemistry of the side chains to be as shown in Figure 1.

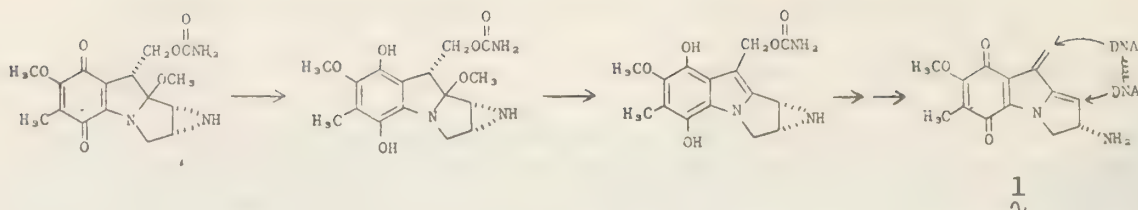
Figure 1



	X	Y	R
Mitomycin A	OCH ₃	OCH ₃	H
Mitomycin B	OCH ₃	OH	CH ₃
Mitomycin C	NH ₂	OCH ₃	H
Porfiromycin	NH ₂	OCH ₃	CH ₃

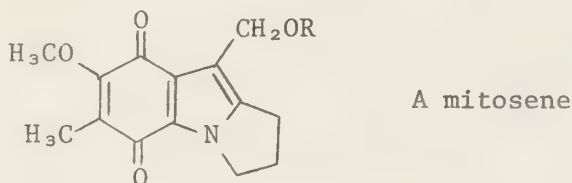
Labeling experiments by Hornemann have shown that a number of compounds, including glucosamine and pyruvate, are precursors to the mitomycins.^{7,8,9} A preliminary scheme for the biosynthetic pathway has been proposed by Lown et al.¹⁰

The biological activity of the mitomycins varies widely. Mitomycin C is a broad spectrum antibacterial and antitumor agent, but the other members are only to some degree useful as bacteriocides. Early investigators have shown that mitomycin C could intercalate the base pairs of DNA¹¹ and that it inhibited DNA biosynthesis.¹² However, intercalation is not the major mechanism of action of the biological activity.¹³ The present evidence indicates the mitomycins are activated by enzymatic reduction of the quinone. This allows elimination of methanol, opening of the aziridine and elimination of the carbamoyl group to give a potent dialkylating agent (1). The intermediate (1) could undergo nucleophilic attack at C-10 and then C-1, presumably by the 6-oxygen of guanine residues on different DNA strands. This can then cross-link the DNA strands and prevent further replication.¹⁴⁻¹⁸ Mitomycin C is presently widely used in Japan, in spite of its high toxicity (LD₅₀ 1-2.5 mg/kg),¹⁹ as an antitumor drug.²⁰ Unfortunately, extensive modification and synthetic

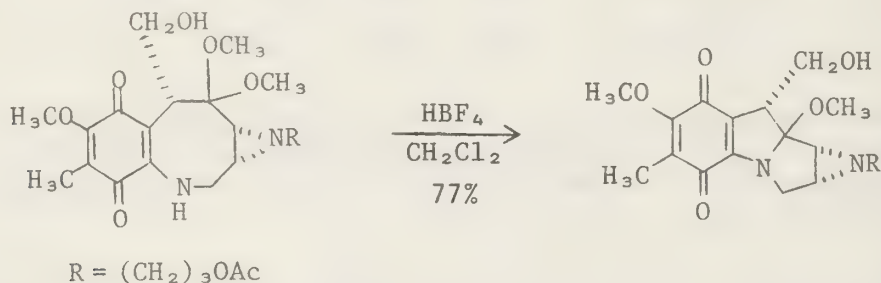


effort has not resulted in an analogue possessing good antibiotic activity and low toxicity.^{20,21}

The mitomycins present quite a challenge for synthetic chemists; synthesis would have to overcome various hurdles, especially the construction of the pyrroloindole ring system, its oxidation to the p-quinone, and introduction of the carbamoyl at C-10, the 9a methoxy and the fused aziridine ring. The extreme lability of the aziridine and methoxy functionalities have led most investigators to concentrate their attempts on the mitosene derivatives.^{10,22-26}



The synthesis of a mitomycin derivative preserving the 9a methoxy has been accomplished by the Harvard group under Y. Kishi.²⁷ Recently, the total synthesis of porfiromycin and mitomycins A and C has been reported.^{28,29} The key step in these syntheses is the transannular displacement of a methoxy group on a substituted benzazocine, possibly patterned after the proposed biogenetic pathway.¹⁰



Further synthetic work remains in this class of antibiotics. Most important is the development of imaginative synthetic methods for quinone formation, for construction of the aziridine ring and especially for the addition of the elements of methanol to indoles to produce the 9a methoxy functionality characteristic of the mitomycins.

BIBLIOGRAPHY

1. T. Hata, Y. Sano, R. Sugawara, A. Matasumae, K. Kanamori, T. Shima, and T. Hoshi, *J. Antibiotics* (Tokyo), Ser. A, 9, 141 (1956).
2. S. Wakaki, H. Marumo, K. Tomioka, G. Shimizu, E. Kato, H. Kamada, S. Kudo, and Y. Fujimoto, *Antibiot. and Chemother.*, 8, 228 (1958).
3. C. DeBoer, A. Dietz, N. E. Lummis, and G. M. Savage, *Antimicrobial Agents Ann.*, 17 (1960).

4. D. V. Lefemine, M. Dann, F. Barbatschi, W. K. Hausmann, V. Zbinovsky, P. Monnikendam, J. Adam, and N. Bohonos, *J. Am. Chem. Soc.*, 84, 3184 (1962).
5. J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Brosschard, W. E. Meyer, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, 84, 3185 (1962).
6. A. Tulinsky, *J. Am. Chem. Soc.*, 84, 3188 (1962).
7. U. Hornemann, J. P. Kehrner, C. S. Nunez, and R. L. Ranieri, *J. Am. Chem. Soc.*, 96, 320 (1974).
8. U. Hornemann and M. J. Aikman, *J. Chem. Soc. Chem. Commun.*, 88 (1973).
9. U. Hornemann, J. P. Kehrner, and J. H. Eggert, *J. Chem. Soc. Chem. Commun.*, 1045 (1974).
10. J. W. Lown and T. Itoh, *Can. J. Chem.*, 53, 960 (1975).
11. M. Kodama, *J. Biochem.*, 61, 162 (1967).
12. M. Sekiguchi and Y. Takagi, *Nature*, 183, 1134 (1959).
13. A. Falaschi and A. Kornberg, *Federation Proc.*, 23, 940 (1964).
14. V. N. Iyer and W. Szybalski, *Science*, 145, 55 (1964).
15. S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, T. Takahashi, S. Wakaki, and M. Matsui, *Proceedings of the 6th International Congress of Chemotherapy*, Vol. II, 1058 (1970).
16. H. S. Schwartz, J. E. Sondergren, and F. S. Philips, *Science*, 142, 1181 (1963).
17. M. Tomasz, C. M. Mercado, J. Olson, and N. Chatterjee, *Biochemistry*, 13, 4878 (1974).
18. H. W. Moore, *Science*, 197, 527 (1977).
19. F. S. Philips, H. S. Schwartz, and S. S. Sternberg, *Cancer Res.*, 20, 1354 (1960).
20. H. Blank and H. Struhal, "Die Antibiotica", Band III, Verlag Hans Carl, Nuremberg, Germany, 1970, p. 412.
21. M. J. Weiss, G. S. Redin, G. R. Allen, Jr., A. C. Dornbush, H. L. Lindsay, J. F. Poletto, W. A. Remers, R. H. Roth, and A. E. Sloboda, *J. Med. Chem.*, 11, 742 (1968).
22. For synthesis of 7-methoxymitosene, see G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, 30, 2897 (1965).
23. S. Danishefsky and R. Doehner, *Tetrahedron Lett.*, 35, 3029, 3031 (1977).
24. J. Rebeck, Jr., and J.-C. E. Gehret, *Tetrahedron Lett.*, 35, 3027 (1977).
25. K. J. Falci, R. W. Franck, and G. P. Smith, *J. Org. Chem.*, 42, 3317 (1977).
26. T. Kametani, T. Ohsawa, K. Takahashi, M. Ihara, and K. Fumumoto, *Heterocycles*, 4, 1637 (1976).
27. F. Nakatsubo, A. J. Cocuzza, D. E. Keely, and Y. Kishi, *J. Am. Chem. Soc.*, 99, 4835 (1977).
28. F. Nakatsubo, T. Fukuyama, A. J. Cocuzza, and Y. Kishi, *J. Am. Chem. Soc.*, in press.
29. T. Fukuyama, F. Nakatsubo, A. J. Cocuzza, and Y. Kishi, submitted for publication in *J. Am. Chem. Soc.*

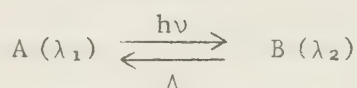
MECHANISMS OF PHOTOCHROMISM IN ORGANIC COMPOUNDS

Reported by Jimmie Smith

November 28, 1977

The phenomenon in which a solid changes color when exposed to light but reverts back to its original color in the dark was called phototropy in the early history of the field.¹ A more descriptive and desirable term has evolved in recent years. This term is photochromism which literally means a coloration by light. Photochromism is defined as a reversible change of a single chemical species between two states having distinguishably different spectra, such changes being induced in at least one direction by the action of electromagnetic radiation. This definition is represented by Scheme I, where λ represents two different maxima.

Scheme I

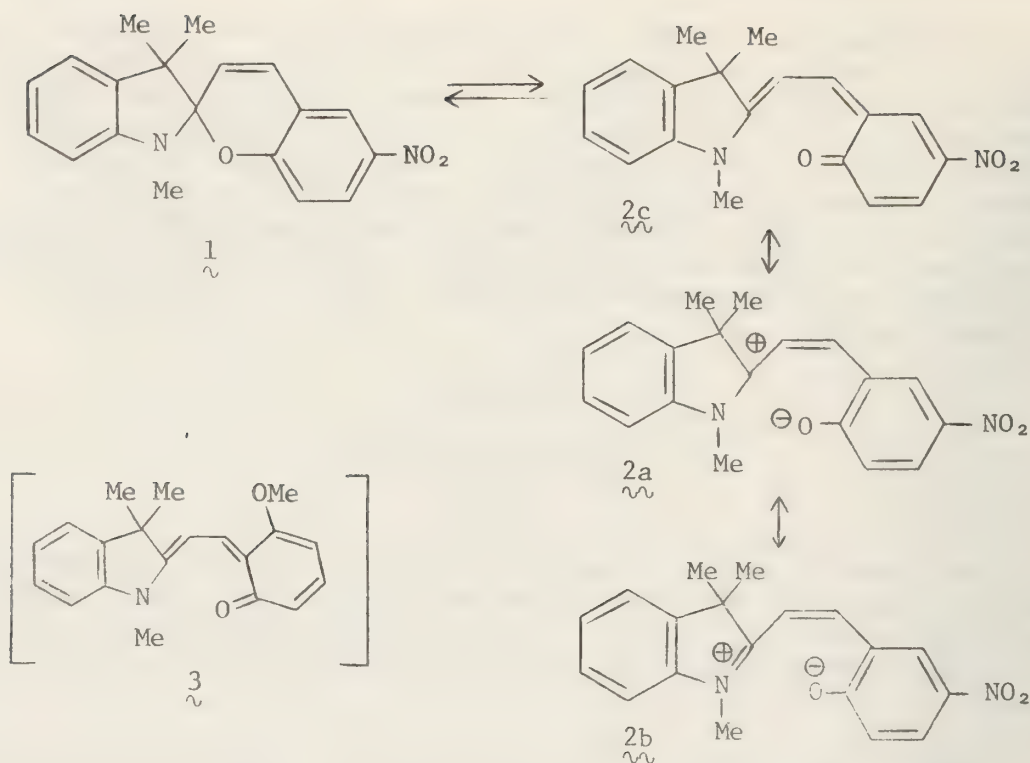


The chemical species A can be a molecule or an ion. The product B may be a single chemical species, or more than one species, provided that they recombine to form A. Usually, species B is in its ground electronic state, thermodynamically less stable and more deeply colored than A.

Photochromism occurs in a wide variety of organic and inorganic compounds. Some classes of organic compounds in which it occurs are hydrazones, osazones, semicarbozones, stilbene derivatives, succinic anhydrides, sydnone, and certain conjugated spiropyrans.^{2,3,4} The mechanism of the photochromic processes include heterolytic cleavage, homolytic cleavage, cis trans isomerization and tautomerization. The discussion that follows will describe the mechanisms using classes of organic compounds typical for the particular mechanism.

Heterolytic Cleavage. Probably the most extensively studied organic photochromic compounds are the spiropyrans (e.g. 1). The nature of the colored form of spiropyran 1 in solution has been widely discussed.⁵ The spectroscopic identity of the photochromic form was first observed by Hirschberg and Fisher.⁶ It is generally assumed that an equilibrium exists between the spiropyran and a planar, colored transient resulting from scission of the bond between the spiro carbon and pyran oxygen. Thus, the highly colored transient is formed as the result of rehybridization of the spiro carbon from sp^3 to sp^2 to give coplanar rings; this is in contrast to the noncoplanarity of rings in the spiropyrans (see Scheme II). The similarity in absorption spectra of the colored form to that of the nonionic merocyanine dye 3 was used to assign 2 as the structure of the colored transient formed upon irradiation. Recent evidence from spectroscopic studies supports the zwitterionic structures as the predominant contributor of the colored transient.^{5,8} That the colorless form of the spiropyran 1 possesses the spiro structure can be shown by ¹HNMR spectroscopy. The peaks representing the gem-dimethyl groups appear at 1.19 and 1.30 ppm as two separate singlet peaks. This suggests that the adjacent carbon atom bears two different substituents which shield the methyl groups' protons to different extents. The N-methyl peak appears at 2.74 ppm, which compares well with the position of 2.70 ppm found for 1,2,3,3-tetramethylindoline.⁷

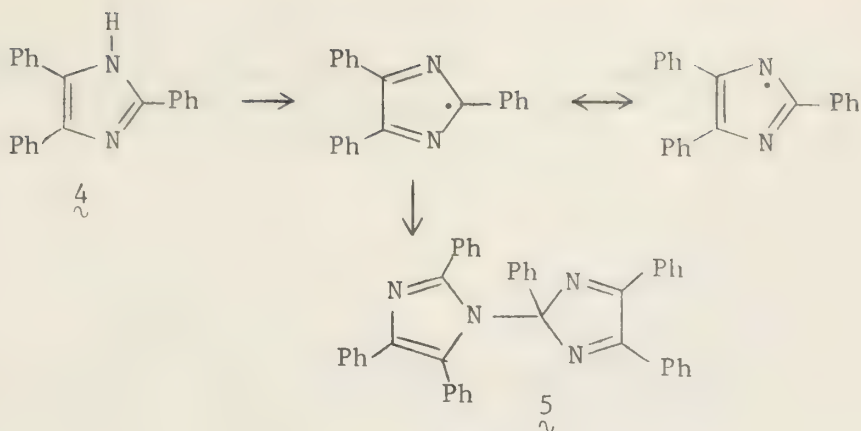
Scheme II



Evidence that the colored species possesses an open structure is shown by its NMR spectrum. The gem-dimethyl groups appear as one singlet at 1.25 ppm. The N-methyl peak of the colored form is shifted downfield to 4.12 ppm, as compared to 2.74 ppm for the N-methyl group in 1. This suggests that the methyl group is attached to a nitrogen atom bearing a partial positive charge.⁵

It has also been observed that as the polarity of the solvent is increased, the visible absorption maximum of the colored form shifts to shorter wavelengths, the extinction coefficient decreases, and the half-width of the band increases. Most convincingly, it has been shown that the rate of formation of the colored form is enhanced by use of polar solvents and slower reversion rates observed by the presence in the spiro compound of electron donating substituents that act to stabilize a positive charge on the heteroatom or the spiro carbon atom; a similar effect was observed by the presence of electron attracting substituents that act to stabilize a negative charge on the pyran oxygen atom.⁷

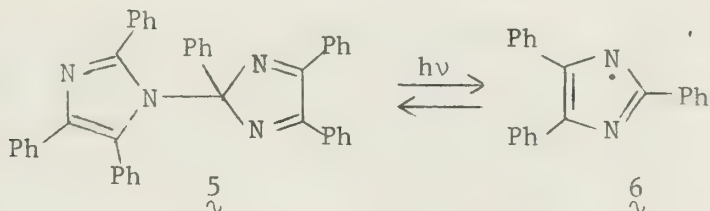
Homolytic Cleavage. Bis-imidazoles, formed by mild oxidation of the parent imidazole with potassium ferricyanide in alkaline solution, are a class of compounds that exhibit photochromism and thermochromism in solution and in solids. This light-induced color change was first observed by Hayaski and Maeda during the investigation of the chemiluminescence of lophine 4.^{9,10}



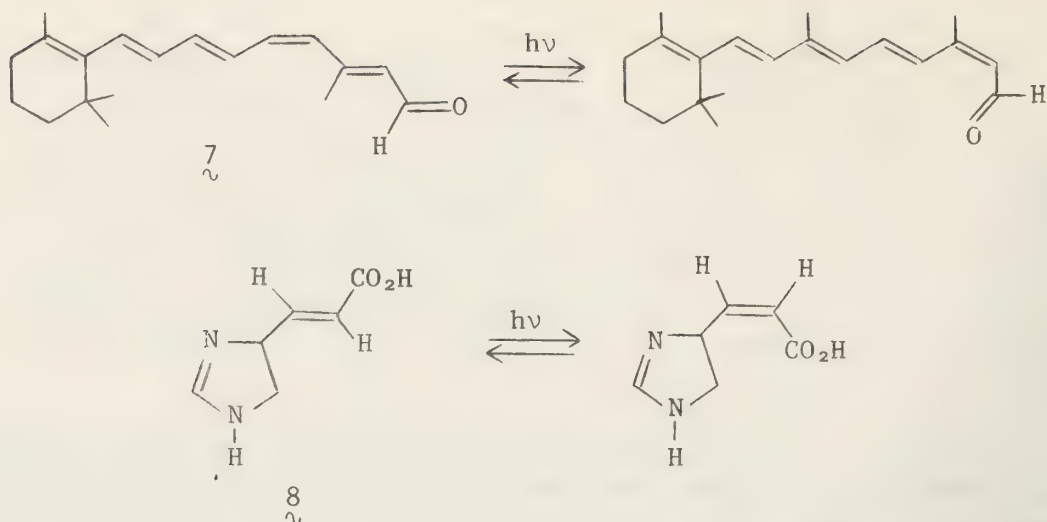
A yellow solution of the dimer 5 gave no ESR signal in the dark at room temperature, whereas the solution produced by irradiation at room temperature showed an ESR signal with a value of g 2.003¹⁰ and a line width of 9.1-Gauss peak to peak. The colored solution upon standing in the dark at room temperature showed a gradual loss of ESR signal intensity. This decrease corresponded to the decrease of the absorbance in the visible region.

Radical formation in the photochromic system was also confirmed by chemical evidence. When a yellow solution of 5 was brought in contact with oxygen under irradiation, a reddish-purple color formed that slowly faded with the absorption of oxygen. The compound was thought to be peroxidic because of liberation of gas upon melting and liberation of iodine from potassium iodide in an acid solution.¹¹ Evidence for a radical mechanism was also observed when an ethanolic solution of the dimer 5, upon irradiation for five days, produced lophine 4 and acetaldehyde. Acetaldehyde was thought to arise from ethanol by reaction with the radical formed under irradiation.¹² The decay of the photochromic form, measured by following the absorption in benzene solution, follows second order kinetics with an energy of activation of 7.3 kcal/mole.

The above description of the system suggests a simple dissociation mechanism for the photochromism of the dimer 5 in solution.



Cis-Trans Isomerization. The photo-induced cis trans isomerization of an organic molecule about an unsaturated linkage is a phenomenon that has been recognized for some time. In at least two cases, this type of reaction can be said to be part of everyone's daily life. The isomerization of rhodopsin (the Schiff base of 11-cis retinol 7 with the ϵ -amino group of a lysine residue in the protein opsin) to "pre-lumirhodopsin" (all trans) is believed to be the primary act in the detection of light by the retina,¹³ and the trans \rightarrow cis isomerization of uracanic acid 8 in the epidermis has been suggested as a mechanism by which part of the harmful energy of ultraviolet radiation is dissipated by the body.^{14,15}



In most cases, especially those involving molecules that isomerize with only a single double bond, the differences in absorption spectra, and thermal stabilities of the two isomers are sufficiently great that accurate measurements of rates, quantum yields and thermodynamic properties can be made without difficulty.

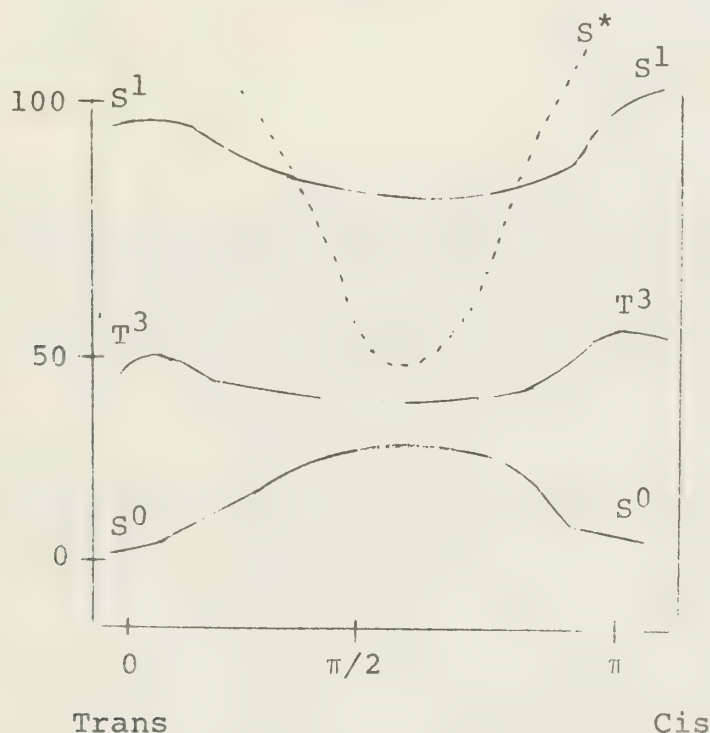
Although not considered bona fide photochromic substances because they have no absorption in the visible portion of the spectrum, the stilbenes represent the most thoroughly studied class of molecules that undergo reversible cis-trans isomerization about a double bond. An early mechanism, proposed by Lewis,^{16,17} was suggested for the isomerization in which molecules passed through a condition of free rotation following conversion from the first excited singlet state. This mechanism has been rejected because any mechanism which involves radiationless internal conversion from an excited singlet state to a high vibrational level would be expected to show a large isotope effect on the rate of internal conversion. In the direct photolysis of perdeuterio and ordinary stilbene, Saltiel¹⁸ found no isotope effect on the photostationary state or upon the quantum yields of cis to trans and trans to cis conversion.

A second mechanism, proposed by Förster,¹⁹ suggested that photoisomerization of olefins, and stilbenes in particular, proceeds via decay from the first excited singlet state to a common or freely interconverting triplet state. Evidence that eliminates the triplet mechanism as the mode of cis trans isomerization of stilbenes has been provided by azulene quenching studies.²⁰ It was found from this study that azulene had very little effect on the trans:cis ratio for direct photoisomerization. This is not the result expected if the triplet mechanism is operating. The trans:cis ratio should increase with increased azulene concentration.

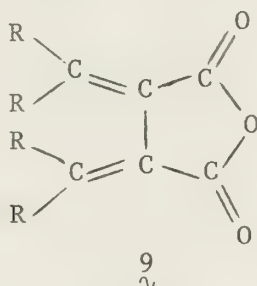
Triplet and ground state mechanisms for direct photoisomerization of stilbene having been rejected, the only remaining reasonable possibility is isomerization in the excited singlet state. The singlet mechanism for isomerization involves rotation of the central bond in the cis and trans excited singlet state to a common twisted singlet state. Irradiation of a trans isomer will produce an excited state molecule which is usually lower in energy than the comparable molecule found from the cis isomer. The energy of the π to π^* excited state is a function of the

angle of twist about the carbon-carbon sigma bond, and trans to cis isomerization is believed to be effected by distortion of the trans excited state to an excited state common to both cis and trans isomers.²¹⁻²³ The mechanism is illustrated in Figure 1.

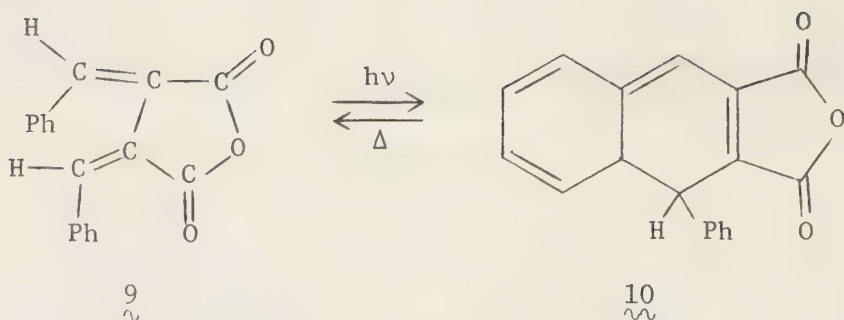
Figure 1



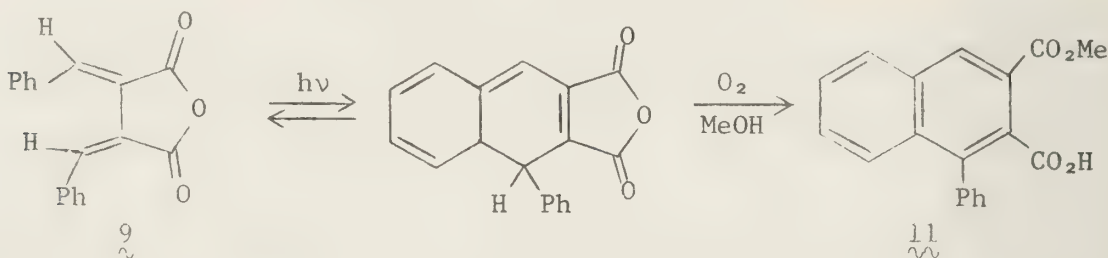
Valence Tautomerism. Among the oldest groups of photochromic compounds are the fulgides, which were extensively investigated by Stobbe²⁴ and Hanel;²⁵ however, the mechanism for the process has been elucidated only in the last ten years by Santiago and Becker.²⁶ Fulgides are derivatives of dimethylene-succinic anhydrides 9.



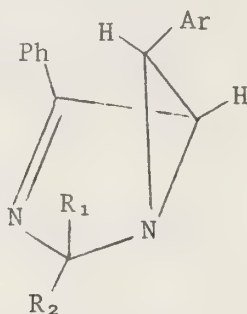
At least one of the substituents R must be aromatic if the compound is to be photochromic. The photogenerated valence tautomer is a dihydronaphthalene derivative 10. The diphenyl fulgides 9 are usually yellow compounds that change to a deeper orange or red upon irradiation. The photocolored species can be identified by characteristic absorption maxima at or near 485 nm in contrast to the colorless forms that show absorption bands at 285 and 355 nm.



Evidence for the mechanism of the photocoloration of 9 was reported by Santiago and Becker.²⁶ These workers found that upon irradiation of a degassed methanolic solution of diphenylfulgide 9 at room temperature and admitting oxygen to the system caused both bleaching and formation of naphthalene derivative. The oxidation product isolated was the acid ester of 1-phenyl-2,3-naphthalenedicarboxylic acid 11.



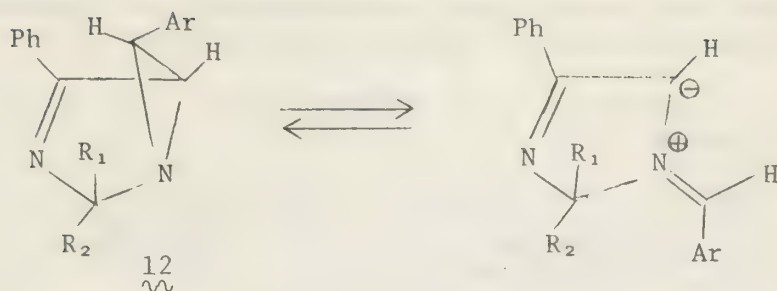
Another class of interesting photochromic compounds are the aziridines.³³ Typical of the compounds investigated is 12. Crystals of 12 upon exposure to light rapidly develop an intense blue color. In the



$R_1 = R_2 = \text{Me}$; $\text{Ar} = \text{p-nitrophenyl}$

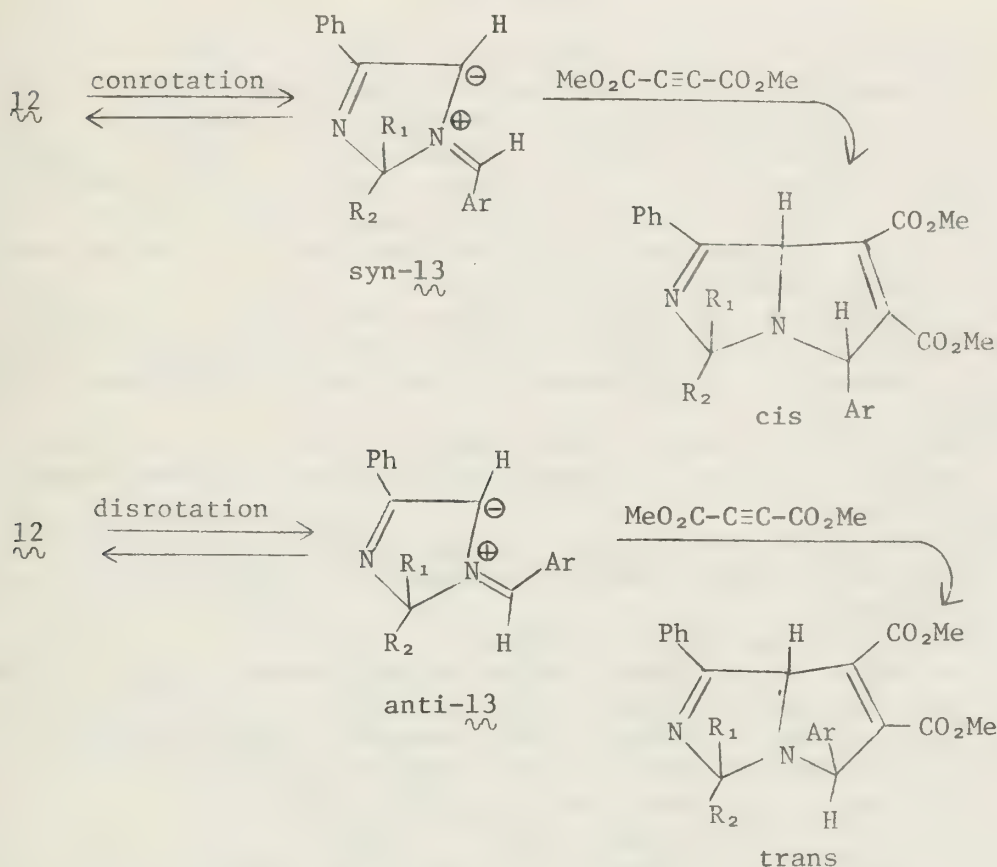
dark at room temperature, the color fades in 12 hr in a first-order kinetic process and the coloration-erasure cycle could be repeated several hundred times with no sign of decomposition. The colored form has been described as having a 1,3 dipolar structure (see Scheme III). In agreement with the dipolar structure, the stability of the colored intermediate is strongly influenced by both electronic and steric changes in the structure of the aziridines. Removal of a nitro group or shifting it to a meta position reduces the photochromic sensitivity of the aziridine.

Scheme III



Orbital symmetry considerations suggest aziridines interconvert with azomethine ylides by a conrotatory process in the ground state. The two possible ylides derived from 12 are syn and anti 13 (Scheme IV).

Scheme IV

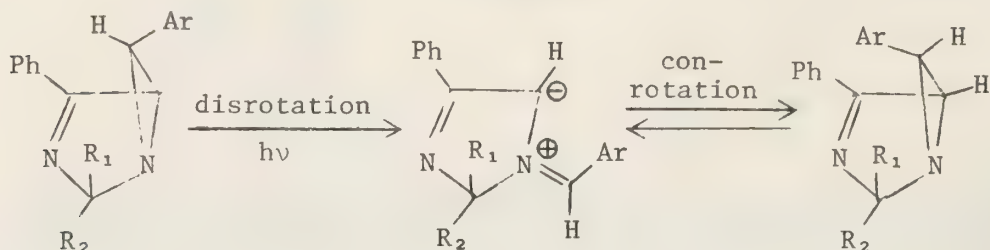


From an earlier study, a cis configuration was assigned to the cyclo-product of 13 with dimethyl acetylenedicarboxylate.³⁴ From the stereochemistry of the adduct, the syn structure was given to the colored intermediate. Consequently, the ring opening appears to involve a conrotation which is a symmetry-allowed concerted process.

The photochemical reaction may be only a dark reaction in which electronically excited states internally convert to vibrationally excited ground states. Support for this view is found from its thermal behavior. Thus, heating 12 produced the same blue color. Furthermore, thermal

cycloaddition gave adducts having the same stereochemistry. If the photochemical ring opening were taking place by a disrotatory process, thermal ring closure would be expected to take an opposite course (See Scheme V). Such exo-endo isomerization has not been observed.

Scheme V



BIBLIOGRAPHY

1. E. J. Bowen, Discussions Faraday Soc., 14, 143 (1953).
2. G. H. Brown and W. G. Shaw, Rev. Pure Appl. Chem., 11, 2 (1961).
3. R. Exielby and R. Grinter, Chem. Rev., 65, 247 (1965).
4. S. D. Cohen and G. H. Newman, J. Photogr. Sci., 15, 290 (1967).
5. (a) J. B. Flannery, Jr., J. Am. Chem. Soc., 90, 5660 (1968); (b) J. Kolc and R. S. Becker, J. Phys. Chem., 71, 4045 (1967); (c) V. A. Kuzmin, Y. N. Malkin, G. G. Dyadyusha, and F. A. Mikhailenko, Dokl. Akad. Nauk SSSR, 223, 127 (1975).
6. Y. Hirschberg and E. Fisher, J. Chem. Soc., 297, 3129 (1954).
7. N. W. Tyler and R. S. Becker, J. Am. Chem. Soc., 92, 1289 (1970).
8. D. A. Reeves and F. Wilkinson, J. Chem. Soc. Faraday Trans. 2, 69, 1381 (1972).
9. T. Hayashi and K. Maeda, Bull. Chem. Soc. Jap., 33, 565 (1960).
10. T. Hayashi, K. Maeda, S. Shida, and K. Nakada, J. Chem. Phys., 32, 1568 (1960).
11. K. Maeda and T. Hayashi, Bull. Chem. Soc. Jap., 43, 429 (1970).
12. T. Hayashi, K. Maeda, and M. Merinaga, Bull. Chem. Soc. Jap., 37, 1563 (1964).
13. G. Wald, Science, 162, 230 (1968).
14. H. P. Baden, M. A. Pathak, and D. Butler, Nature, 210, 732 (1966).
15. F. Daniels, Jr., Sci. Amer., 219, 38 (1968).
16. G. N. Lewis and M. Kasha, J. Am. Chem. Soc., 66, 2100 (1944).
17. G. N. Lewis and M. Kasha, J. Am. Chem. Soc., 67, 994 (1945).
18. J. Saltiel, J. Am. Chem. Soc., 90, 6394 (1968).
19. T. Förster, Z. Elektrochem., 56, 716 (1952).
20. J. Saltiel and E. D. Megarity, J. Am. Chem. Soc., 94, 2742 (1972).
21. G. S. Hammond, J. Saltiel, A. A. Lamsla, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, J. Am. Chem. Soc., 86, 3197 (1964).
22. M. C. Bruni, F. Momicchioli, I. Baraldi, and J. Langlet, Chem. Phys. Lett., 36, 484 (1975).
23. G. Orlandi and W. Siebrand, Chem. Phys. Lett., 30, 352 (1975).
24. H. Stobbe, Ber., 37, 2236 (1904).
25. L. Hänel, Naturwissenschaften, 37, 91 (1950).
26. A. Santiago and R. S. Becker, J. Am. Chem. Soc., 90, 3654 (1968).
27. I. Gruda and R. M. Leblam, Can. J. Chem., 54, 576 (1976).
28. R. J. Hart, H. G. Heller, R. M. Megit, and M. J. Szweczyk, J. Chem. Soc. Perkins Trans. 1, 22, 2227 (1975).

29. A. A. Parshutkui and V. A. Krongauz, Mol. Photochem., 6, 437 (1974).
30. J. M. McBride and G. T. Evans, Chem. Phys. Lett., 36, 41 (1975).
31. D. A. Reeves and F. Wilkinson, J. Chem. Soc. Faraday Trans. 2, 69, 1381 (1973).
32. G. H. Brown (editor), Photochromism, New York, Interscience (1971).
33. H. W. Heine, R. W. Weese, R. A. Cooper, and A. J. Durbetaki, J. Org. Chem., 32, 2708 (1967).
34. T. DoMink and A. M. Trozzolo, J. Am. Chem. Soc., 92, 6997 (1970).

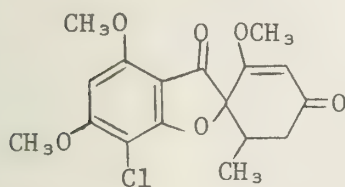
BIOGENETIC-TYPE SYNTHESIS OF POLYKETIDES

Reported by Susan Wells

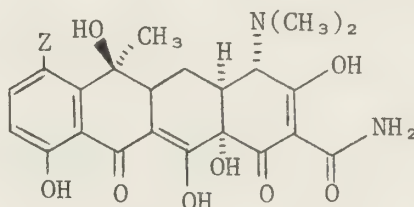
December 1, 1977

Biogenetic-type syntheses are laboratory preparations patterned after biosynthetic routes (proven or hypothetical) to natural products. Van Tamelen has written an excellent defense of such syntheses,¹ emphasizing their requirements, uses, and limitations. Three points should be noted: the starting materials may differ from the "natural" ones in minor aspects; the reactions may be carried out under non-physiological conditions (to compensate for lack of enzyme control and catalysis); and the products need not be identical to the natural product target, but must contain the main structural features (i.e. differ only in modifications of functional groups).

Polyketides are a diverse group of secondary metabolites found mostly in fungi, lichens, and ferns.^{2a,b} They are noted for their large degree of functionalization: aromatic rings and oxygen-containing functional groups on alternant carbons are especially prominent. Many, such as griseofulvin (1), tetracycline (2a), and aureomycin (2b), have antifungal or antibiotic activity.



1

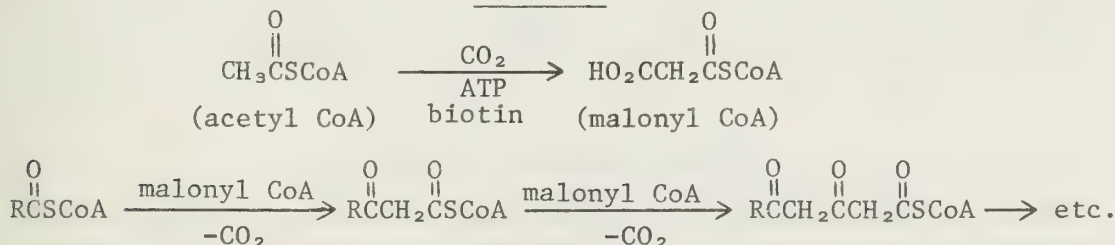


2 a : Z = H
2 b : Z = Cl

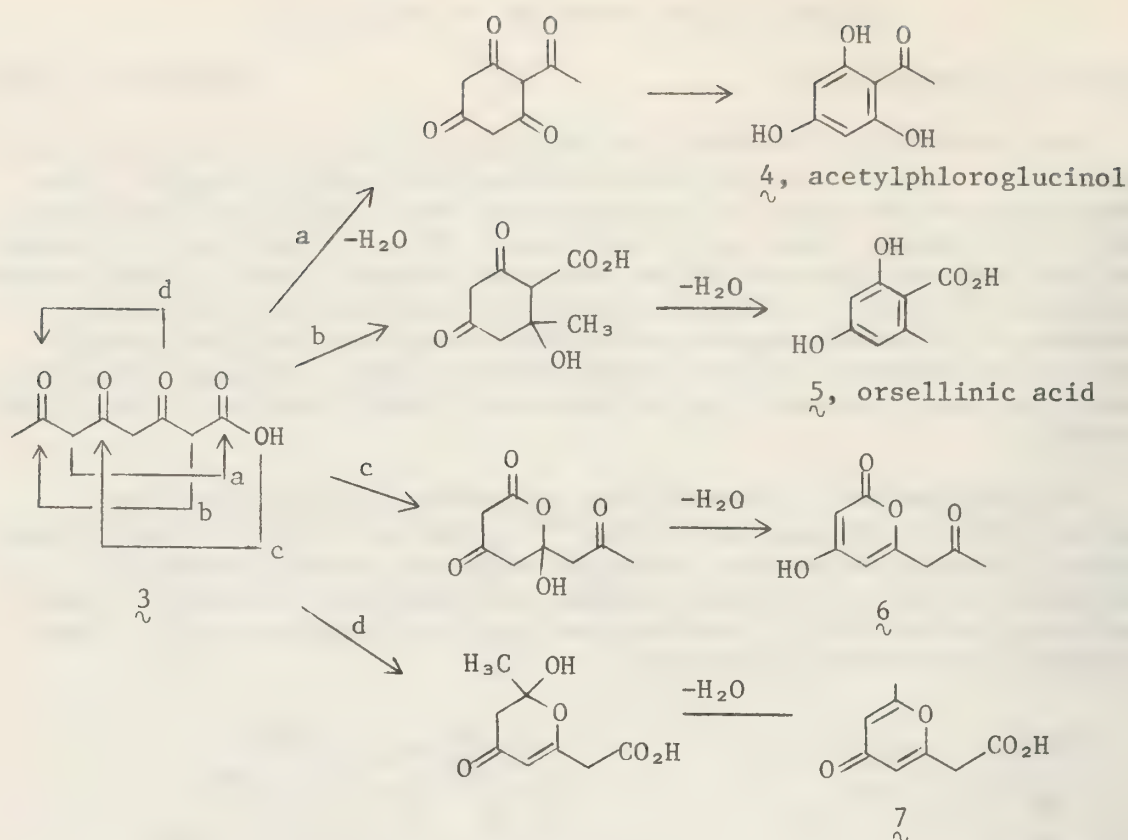
Biosynthesis

The fundamental relationship between these compounds lies in their biosynthetic origins. The "polyketide hypothesis" was first suggested (and named) by Collie; later, Birch further developed the ideas with greater experimental support.^{2c} Polyketides are biosynthesized from acetate via β -polycarbonyl intermediates (Scheme I). These intermediates can subsequently cyclize via intramolecular aldol and Claisen condensations to give a variety of aromatic and heterocyclic derivatives. Scheme II

Scheme I

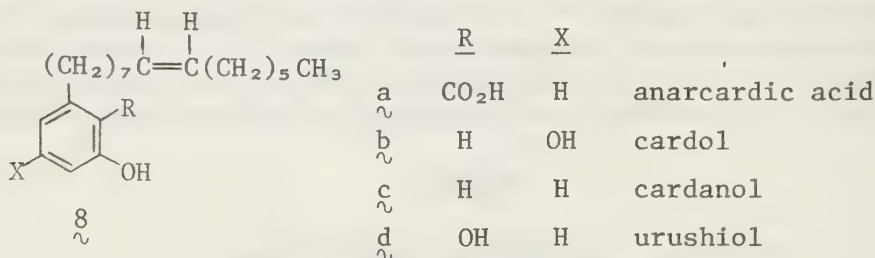


summarizes these reactions for the simplest case, that of a triketide acid, 3. Presumably, these reactions would be occurring on an enzyme "template" to direct the formation of a specific product. Longer polyketide chains can repeat this process, generating polycyclic compounds.²



Scheme II

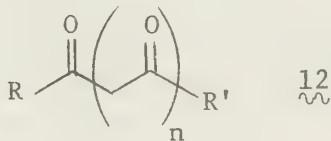
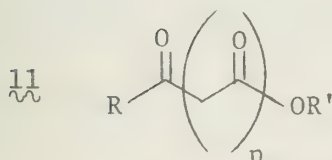
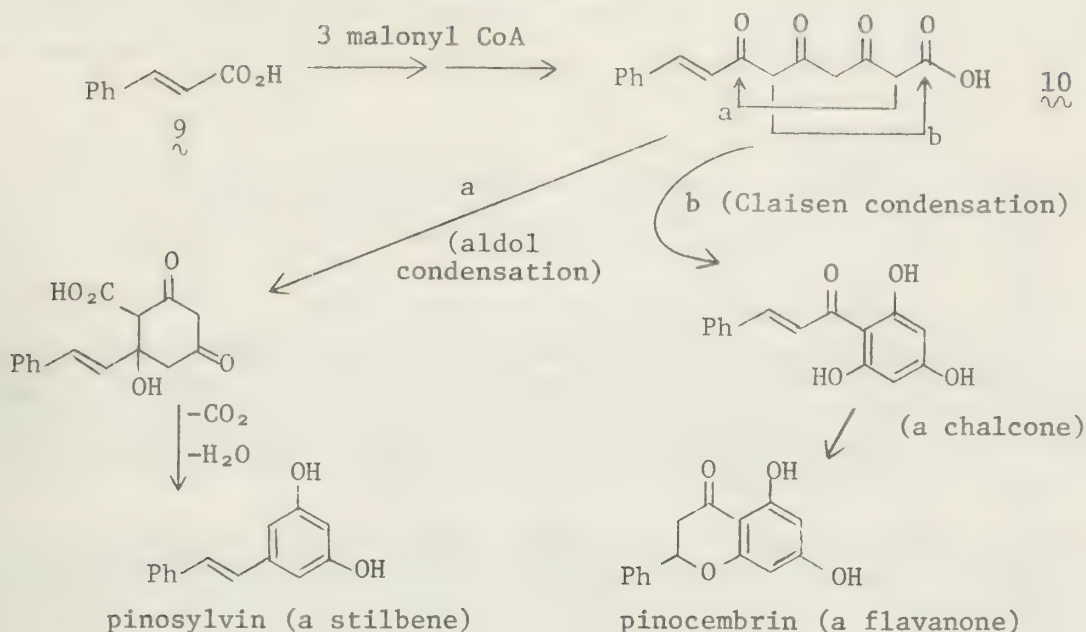
The final polyketide metabolites do not always have exactly the predicted functionality. Common changes include additional methyl groups, oxidation, halogenation, loss of oxygen, and decarboxylation. These modifications are enzyme-mediated and may occur on either the β -polycarbonyl intermediate or the cyclization product.²⁻⁴ In addition, the starter unit does not have to be acetate. The Anacardiaceae (poison ivy) irritants (8) have an unsaturated C_{16} fatty acid (e.g., palmitoleic acid, $Z-\Delta^9$)[~] starter unit.^{2a,d} A phenylpropenoic acid (9) starter unit can yield stilbenes or flavonoids upon cyclization (Scheme III).^{2a,d,4,5}



Biogenetic-Type Syntheses

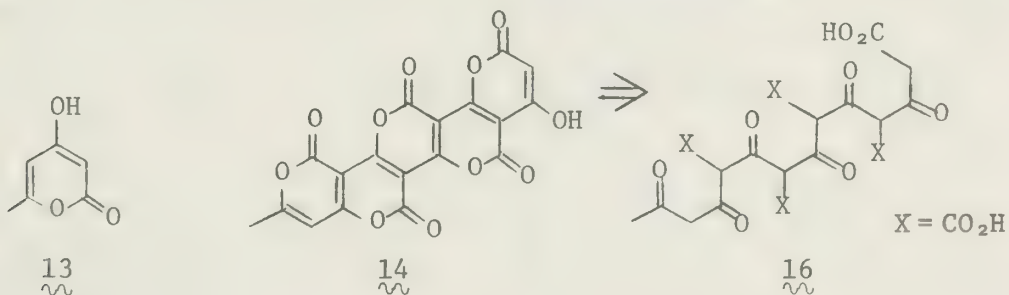
The first challenge that arises in the biogenetic-type synthesis of polyketides is the formation of the somewhat unstable β -polycarbonyl intermediate, either an acid or ester (11) or ketone (12). Once this intermediate is constructed, the problem of stereospecific cyclization must be solved. Since Harris has reviewed the literature on this subject through 1972,⁴ this seminar will concentrate on work published since then.

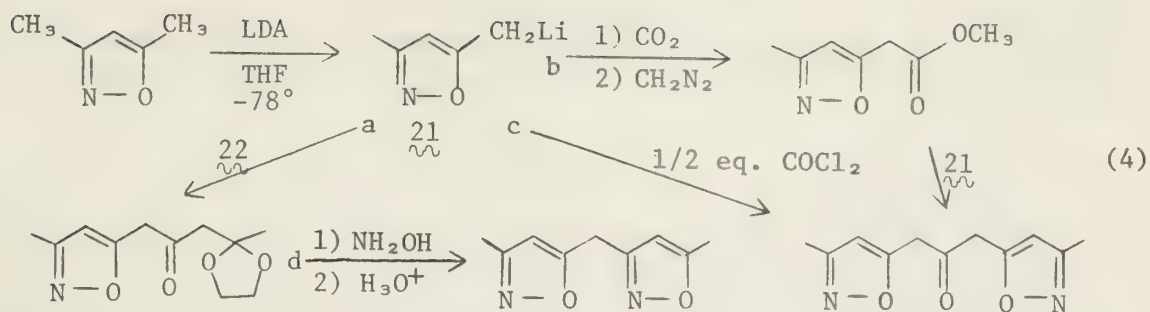
Scheme III



1. Protected β -Polycarbonyl Compounds. Harris, Weiler, and their co-workers have succeeded in synthesizing free β -polycarbonyl compounds, but much work, including most of the early work, has concentrated on synthesis of protected forms of these compounds. A major drawback to using protected polyketides is that the conditions required to remove the protecting groups are the same as those that promote cyclizations of the free polyketide. Thus, only cyclization products are isolated.

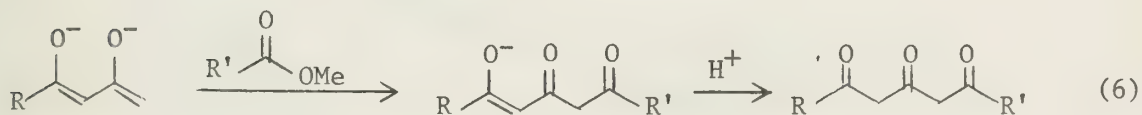
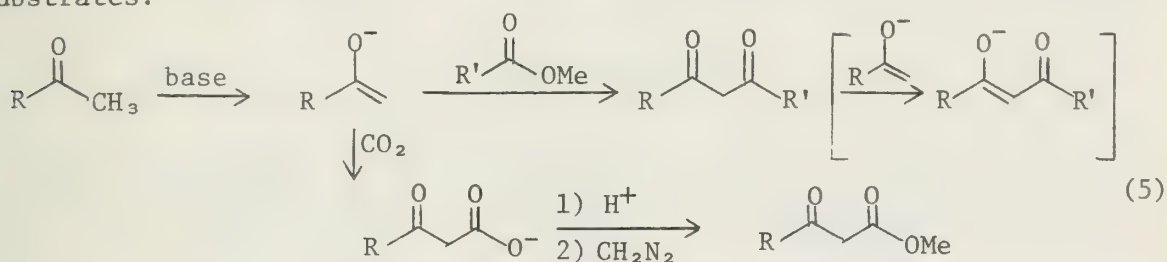
The first class of masked polyketides to be studied was the 4-hydroxy-2-pyrones.^{4,6} No new work on these compounds has appeared since publication of the reviews of Money⁶ and Harris,⁴ and only a brief outline of their synthesis will be given here. The studied pyrones range from triacetic acid lactone (13), first studied by Collie in the 1890's, to pentapyrone 14, synthesized by Scott's group in 1971.⁴ The longest β -polycarbonyl equivalent of this type is the protected diacid 15.⁴ The simplest





Tanaka and co-workers have used these methods to make tetra- and hexa-carbonyl equivalents (Eq. 4a,d).¹¹ The Ricca group has prepared the bisisoxazole 20 from dipolar cyclizations (Eq. 3).^{4,10d} They have also synthesized a pentacarbonyl equivalent bisisoxazole via acylation (Eq. 4b, c).^{10g} Flavonoid-type precursors have been synthesized by the same group using an isoxazole-Wittig reagent to create the double bond.^{10e}

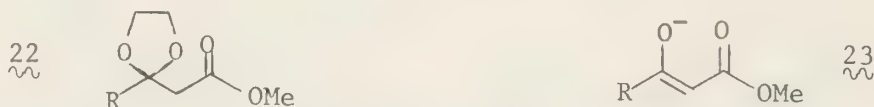
2. Unprotected β -Polycarbonyl Compounds. With the advent of strong bases such as *n*-butyllithium and lithium diisopropylamide, it became possible to synthesize unprotected polyketides with up to eight carbonyls. The method of choice is acylation or carboxylation of an enolate anion (Eq. 5). Longer chains can be synthesized by acylating the dianion of a β -diketone (Eq. 6).^{4,13} Lithium diisopropylamide has proved to be the most convenient strong base to use, since it can be generated in a THF solution.^{4,13} In all cases, acylation occurred at the more nucleophilic terminal enolate.^{4,13,14} Such schemes proved useful for synthesis of polyketides containing up to five carbonyls, employing up to tetra-anion substrates.¹⁵



One difficulty in the synthesis of free polyketides is that the product contains doubly-activated methylene protons that can protonate the terminal enol of the starting material (Eq. 5). This loss of starting material imposes a maximum yield of 50%. Addition of an extra equivalent of strong base during the reaction improves the yield.¹⁵⁻¹⁸ Seebach has chosen instead to add a cold (-78°) solution of the amine-free enolate to the acid chloride, also at -78° .¹⁸

These syntheses suffered greatly from their "linear" nature: each acylation proceeded in 20 to 60% isolated yield, making the overall yield of the larger polyketides quite low. There are two routes available to more efficient "convergent" syntheses. One is to acylate both ends of a β -polyketone.^{4,15} Alternatively, the enolate can be acylated with a β -keto ester or equivalent (22, 23).^{4,15,17} The monoanion of the β -keto ester

(23) must be used to prevent proton exchange with the starting material. Combining these two convergent schemes, Wittek and Harris made free β -hexa-, -hepta-, and -octacarbonyls from the β -di-, -tri-, and -tetraketones, respectively.¹⁵

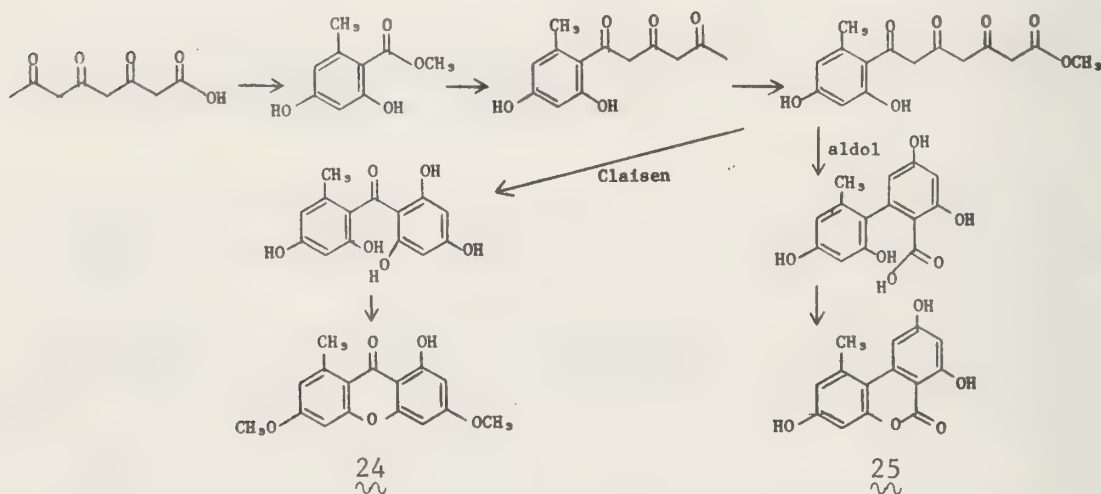


3. Cyclizations. A major problem with biogenetic-type syntheses of polyketide natural products is the difficulty of directing the cyclization of the polyketide chain to a single product. Even a triketo acid can cyclize in four ways (Scheme II). In the simpler systems, careful choice of cyclization reagent and conditions, along with much trial-and-error stumbling, has succeeded in yielding selective cyclizations.⁴ For example, 3,5,7-trioxooctanoic acid (3) can be selectively cyclized to the four products shown in Scheme II.⁴

Cyclization of larger polyketides has largely been an art of choosing the proper reagents and conditions, followed by separation of the isomeric products.⁴ Recently, some solutions of general applicability have been reported in the literature.^{8,19,20}

Harris and Hay focused on natural products containing two independent (*i.e.* non-fused) polyketide-derived rings, such as lichexanthrone (24) and alternariol (25).¹⁹ Their strategy (Scheme IV) was first to synthesize the orsellinic acid-type ring, then elaborate to a longer polyketide, and finally cyclize to either a second orsellinic acid-type ring (25) or an acylphloroglucinol-type ring (24).

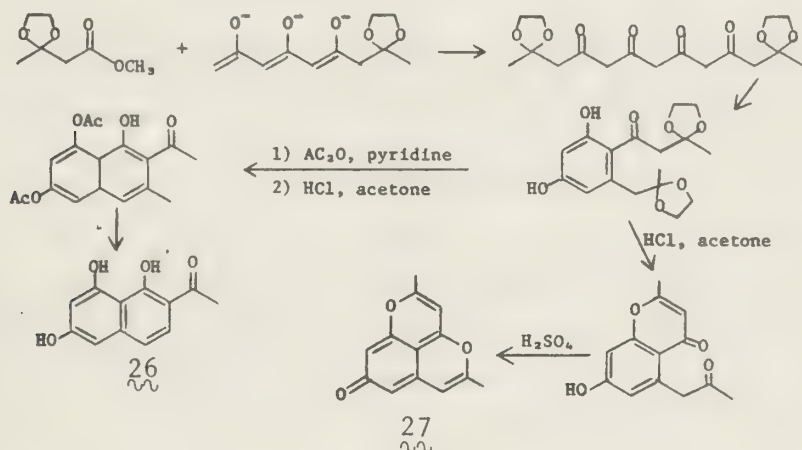
Scheme IV



Protecting groups, such as ketals, have been used to direct cyclizations by effectively shortening the length of the polyketide chain. Using such a strategy, the Harris group has effected the biogenetic-type syntheses of the natural products 6-hydroxymusizin (26), barakol (27), elutherinol (28), and emodin (29).⁸ Scheme V outlines the synthesis of the β -hexaketone-derived metabolites.^{8a} When both terminal carbonyls

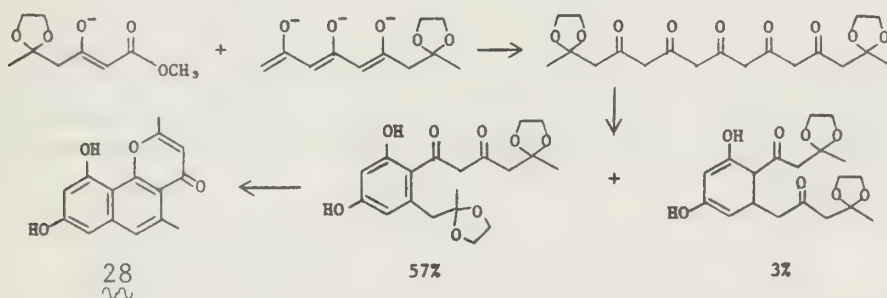
are protected, only one cyclization is possible. The two remaining modes of cyclization, leading to the precursors of 26 and 27, can be effected with different reaction conditions.

Scheme V

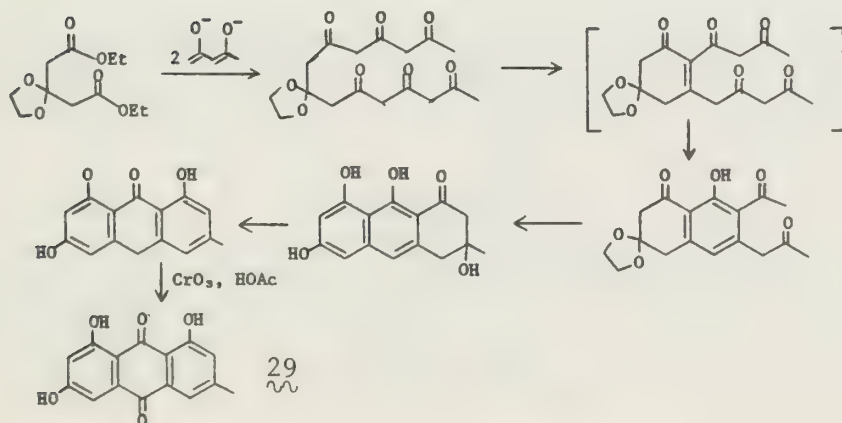


Synthesis of the β -heptaketone-derived metabolites was more difficult. With the two terminal carbonyls protected, there are now two possible initial cyclizations,^{8a} but one of these (precursor to 29) was obtained only in trace amounts (Scheme VI). The major isomer, however, was

Scheme VI



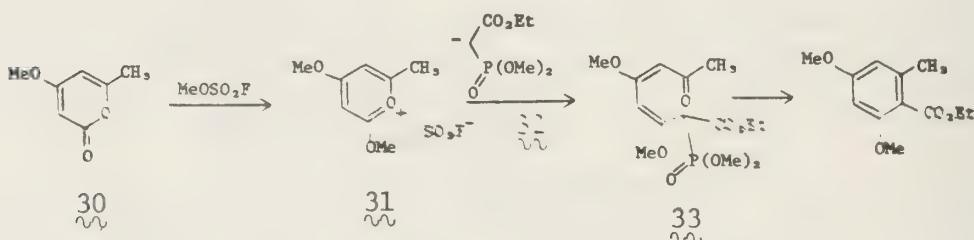
Scheme VII



readily elaborated into 28.^{8a} Directing the initial cyclization with a ketal on the central carbonyl allowed synthesis of 29 (Scheme VII).^{8b}

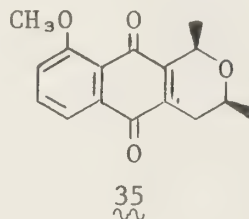
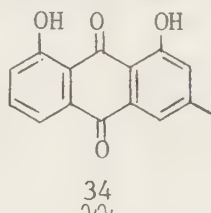
Griffin and Staunton have used a novel Wittig reagent to direct cyclization of a polyketide chain (Scheme VIII).²⁰ Methylfluorosulfonate reacts with triacetic acid equivalent 30 to give the pyrylium salt 31. This salt is then treated with the Wittig reagent 32, furnishing a fourth acetate unit while simultaneously creating a new Wittig reagent (33) that is suitably positioned to give cyclization. Although the product, a derivative of methyl orsellinate, is readily obtained by other means, this idea may be useful in directing cyclization of longer polyketides.

Scheme VIII



4. Modified Polyketide Metabolites. Biogenetic-type syntheses of natural products containing starter units other than acetate have been studied.⁴ An example of such syntheses is that of pinosylvin and pinocembrin accomplished by Harris and Carney⁵ following the biosynthetic pattern outlined in Scheme III. Aldol condensation to pinosylvin was accomplished by treating the acid 10 with a pH 5 buffer. Claisen condensation to pinocembrin required making the methyl ester of 10. Flavonoid-type compounds have also been synthesized by the Ricca group using isoxazoles.^{10e}

Polyketide metabolites having "missing" oxygens can be synthesized by reducing a carbonyl to a double bond (or a synthetic equivalent) before cyclization.⁴ Recent examples include Harris' syntheses of chrysophanol (34)^{8b} and eleutherin (35).²¹



Isoxazoles are uniquely suited for incorporation of nitrogen into the final structure, since the initial hydrogenolysis product is a carbonyl-imine (Eq. 3). Cyclizations of such systems can yield aminophenols.^{10f,22}

BIBLIOGRAPHY

1. E. E. van Tamelen, Fortschr. Chem. Org. Naturst., 19, 242 (1961).
2. (a) T. A. Geissman and D. G. H. Crout, "Organic Chemistry of Secondary Plant Metabolism", Freeman, Cooper & Company, San Francisco, 1969; (b) W. B. Turner, "Fungal Metabolites", Academic Press, New York, 1971; (c) A. J. Birch, Fortschr. Chem. Org. Naturst., 14,

- 186 (1957) and references within; (d) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins", Benjamin, New York, 1964; (e) for recent literature reviews (Specialist Periodical Reports), see T. Money, *Biosynthesis*, 2, 183 (1973), and 4, 1 (1976).
3. The sequence of such modifications in griseofulvin has been studied: C. M. Harris, J. S. Roberson, and T. M. Harris, *J. Am. Chem. Soc.*, 98, 5380 (1976).
 4. T. M. Harris, C. M. Harris, and K. B. Hindley, *Fortschr. Chem. Org. Naturst.*, 31, 217 (1974), and references within.
 5. (a) T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.*, 88, 2053 (1966); (b) T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.*, 88, 5686 (1966); (c) T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.*, 89, 6734 (1967).
 6. T. Money, *Chem. Rev.*, 70, 553 (1970), and references within.
 7. A. J. Birch, P. Fitton, D. C. C. Smith, D. E. Steere, and A. R. Stelfox, *J. Chem. Soc.*, 2209 (1963).
 8. (a) T. M. Harris and P. J. Wittek, *J. Am. Chem. Soc.*, 97, 3270 (1975); (b) T. M. Harris, A. D. Webb, C. M. Harris, P. J. Wittek, and T. P. Murray, *J. Am. Chem. Soc.*, 98, 6065 (1976).
 9. N. Takeuci, M. Murase, K. Ochi, and S. Tobinaga, *J. Chem. Soc. Chem. Commun.*, 820 (1976).
 10. (a) G. Casnati, A. Quilico, A. Ricca, and P. Vita Finzi, *Chim. Ind. (Milan)*, 47, 993 (1965) [*Chem. Abstr.*, 64, 8068 (1966)]; (b) G. Casnati, A. Quilico, A. Ricca, and P. Vita Finzi, *Tetrahedron Lett.*, 233 (1966); (c) G. Casnati, A. Quilico, A. Ricca, and P. Vita Finzi, *Gazz. Chim. Ital.*, 96, 1064 (1966) [*Chem. Abstr.*, 66, 37811 (1967)]; (d) S. Auricchio and A. Ricca, *Gazz. Chim. Ital.*, 103, 37 (1973); (e) P. Bravo, A. Ricca, and O. V. de Pava, *Chim. Ind. (Milan)*, 56, 25 (1974); (f) S. Auricchio, S. Morrochi, and A. Ricca, *Tetrahedron Lett.*, 2793 (1974); (g) S. Auricchio, R. Colle, S. Morrochi, and A. Ricca, *Gazz. Chim. Ital.*, 106, 823 (1976).
 11. T. Tanaka, M. Miyazaki, and I. Iijima, *J. Chem. Soc. Chem. Commun.*, 233 (1973).
 12. A. I. Meyers, "Heterocycles in Organic Synthesis", Wiley, New York, 1974.
 13. For a review of dianion chemistry, see T. M. Harris and C. M. Harris, *Org. React.*, 17, 155 (1969).
 14. T. M. Harris, G. P. Murphy, and A. J. Poje, *J. Am. Chem. Soc.*, 98, 7733 (1976).
 15. P. J. Wittek and T. M. Harris, *J. Am. Chem. Soc.*, 95, 6865 (1973).
 16. S. N. Huckin and L. Weiler, *Tetrahedron Lett.*, 2405 (1972).
 17. (a) T. P. Murray and T. M. Harris, *J. Am. Chem. Soc.*, 94, 8253 (1972); (b) T. M. Harris, T. P. Murray, C. M. Harris, and M. Gumulka, *J. Chem. Soc. Chem. Commun.*, 362 (1974); (c) S. N. Huckin and L. Weiler, *Can. J. Chem.*, 52, 1343 (1974).
 18. A. K. Beck, M. S. Hoeckstra, and D. Seebach, *Tetrahedron Lett.*, 1187 (1977).
 19. T. M. Harris and J. V. Hay, *J. Am. Chem. Soc.*, 99, 1631 (1977).
 20. D. A. Griffin and J. Staunton, *J. Chem. Soc. Chem. Commun.*, 675 (1975).
 21. A. D. Webb and T. M. Harris, *Tetrahedron Lett.*, 2069 (1977).
 22. (a) A. A. Ahkrem, A. M. Moiseenkov, and F. A. Lachwicz, *Tetrahedron*, 29, 1083 (1973); (b) A. A. Ahkrem, A. M. Moiseenkov, and F. A. Lakhvich, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. (Engl. Transl.)*, 22, 1077 (1973).

HYDROLYSIS OF FIVE-MEMBERED CYCLIC PHOSPHATE ESTERS: MECHANISTIC AND ENERGETIC CONSIDERATIONS

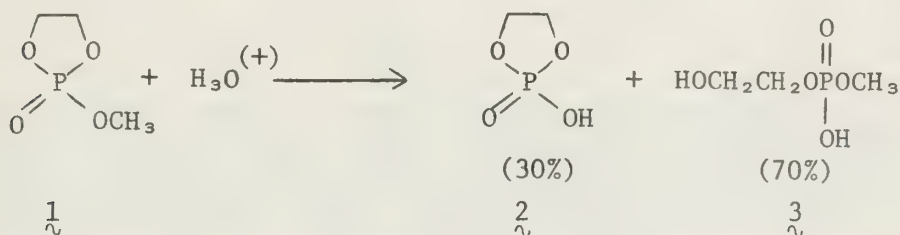
Reported by Linda G. Carter

December 8, 1977

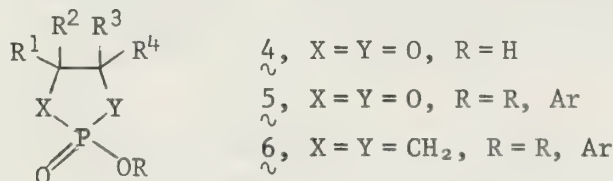
The class of phosphorus compounds, the phosphates, is one of the most widely studied groups in chemistry. Phosphates are involved in essential life processes, are found in compounds having many industrially useful chemical and physical properties, and are studied to provide a clearer understanding of their structure.¹ Perhaps the most common mode of reaction is hydrolysis. This abstract will present a mechanistic explanation for the large rate enhancement observed for five-membered cyclic phosphate esters undergoing hydrolysis.

The acidic hydrolysis of methyl ethylene phosphate (1) in Scheme I illustrates the two possible hydrolytic routes for these cyclic triesters of phosphoric acid.²

Scheme I

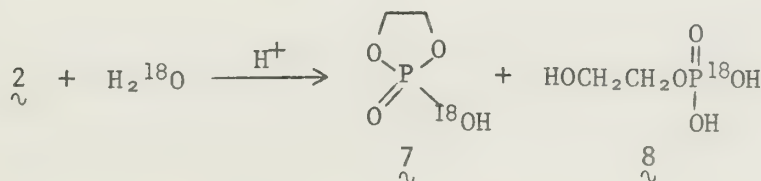


The acidic and alkaline hydrolysis of five-membered cyclic diesters, 4, and triesters, 5, of phosphoric acid proceed 10^6 - 10^8 times faster than their acyclic counterparts.^{2,3} In sharp contrast, the rates of hydrolyses of six- and seven-membered cyclic phosphates proceed with rates similar to their acyclic analogues, while the rates of hydrolysis of simple phosphinates, 6, are not much greater than their acyclic counterparts.³



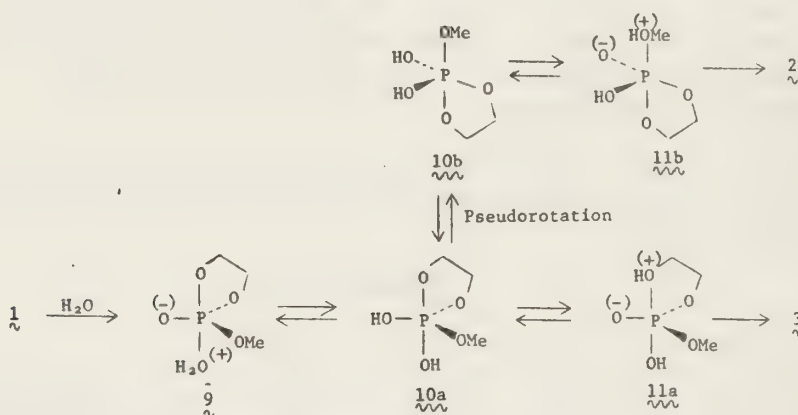
Unlike the hydrolysis of dimethyl phosphate, the hydrolysis of hydrogen ethylene phosphate (2), as shown in Scheme II, is accompanied by rapid oxygen exchange into unreacted substrate to give 7 and by ring opening to afford 8 (the label being distributed among the phosphoryl and hydroxyl oxygens).⁴

Scheme II



What feature can cause the rapid rate of hydrolysis and specific exchange of five-membered cyclic phosphate esters? The answer to the question requires mechanistic analysis. To explain the results of Schemes I and II, Hamer,⁵ Dennis and Westheimer,^{2,6} and later, Ramirez and Ugi⁷ postulated the general mechanism illustrated in Scheme III. This abstract will consider the evidence for this scheme and discuss how this mechanism provides answers to the above question. First the steps in the scheme will be sequentially discussed.

Scheme III



A nucleophilic backside attack along an apical line of one of the P-O bonds, allowing for a minimization of steric and energetic considerations,^{7c,8} would give the trigonal bipyramidal intermediate 9 having the entering group in an apical position. The five-membered ring is postulated to occupy one apical and one equatorial position to allow for minimization of ring strain. Evidence for a trigonal bipyramidal structure of pentacoordinate phosphorus comes from the structure elucidation of numerous monocyclic oxyphosphoranes by x-ray crystallography.⁹ The bond angles shown for phenanthrenequinone-triisopropyl phosphite (12) in Table 1 indicate that the bonding is essentially a trigonal bipyramid with a cyclic O-P-O bond angle of ca. 90°.¹⁰ The ring therefore occupies one apical and one equatorial position. X-ray analysis of many other monocyclic oxyphosphoranes reveals structures similar to 12.⁹

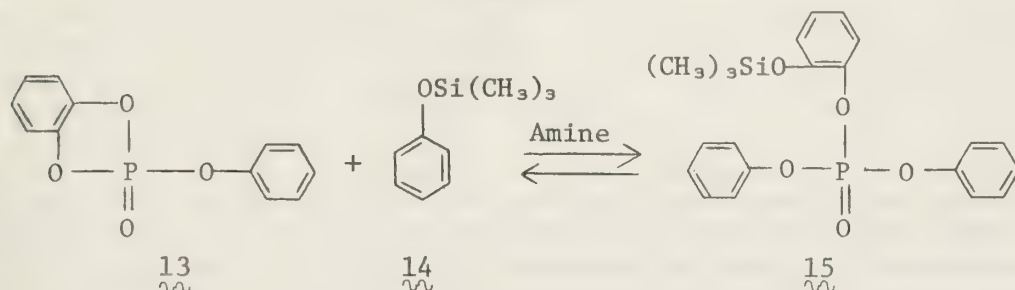
Table 1

Bond length, Å		Bond angle, deg			
P-O ₁	1.753	O ₁ -P-O ₂	89.3	P-O ₁ -C ₁	111.9
P-O ₃	1.649	O ₃ -P-O ₂	88.6	P-O ₂ -C ₂	114.2
P-O ₂	1.641	O ₃ -P-O ₄	91.3	P-O ₃ -C ₃	121.8
P-O ₄	1.601	O ₃ -P-O ₅	93.1	P-O ₄ -C ₄	129.8
P-O ₅	1.586	O ₂ -P-O ₄	117.2	P-O ₅ -C ₅	127.5
O ₁ -C ₁	1.347	O ₄ -P-O ₅	117.2		
O ₂ -C ₂	1.433	O ₅ -P-O ₂	125.5		
C ₁ -C ₂	1.333	O ₁ -C ₁ -C ₂	113.9		
O ₃ -C ₃	1.463	O ₃ -C ₂ -C ₁	110.3		

The trapping of these proposed pentacoordinate intermediates in a sequence involving nucleophilic addition provides further evidence in support of the first step in Scheme III. In accord with Scheme IV, phenyl o-phenylene phosphate (13) has been shown to react reversibly with O-trimethylsilylphenol (14) in aprotic solvents under amine catalysis to

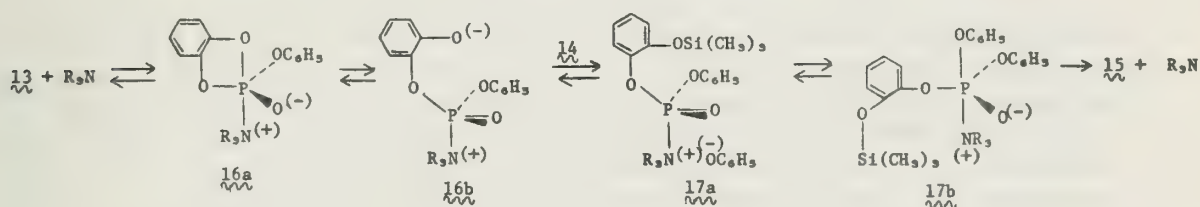
afford diphenyl (2-trimethylsilyloxy)phenyl phosphate (15) which is considered to be in dynamic equilibrium with the reactants.¹¹

Scheme IV



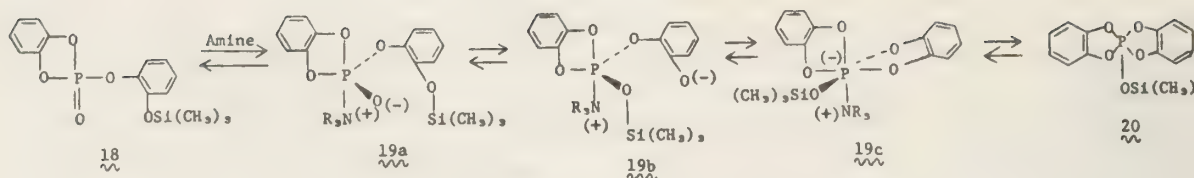
The evidence for the assignment of structures 13 and 15 is based upon ^{31}P and ^1H NMR spectroscopy. In the ^{31}P NMR, 13 exhibits a chemical shift of $\delta-6.2$ (downfield from a H_3PO_4 standard) which is characteristic of cyclic phosphates. The phosphorus chemical shift for 15 is $\delta+16.8$ (upfield from a H_3PO_4 standard), characteristic of acyclic phosphates. The catalytic efficiency was shown to be a function of steric requirements. In control experiments, neither 13 nor 14 was noticeably affected by tertiary amines in absence of the second reactant, thus ruling out any appreciable concentration of a stable complex of a reagent with the amine. Since this phosphate ester, 13, undergoes facile hydrolysis and Scheme IV is amine-catalyzed, there is a high probability that a nucleophilic attack of the amine at the phosphorus center could occur. A mechanism to explain these results of Scheme IV involves the trapping of a pentacoordinate phosphorus intermediate as illustrated in Scheme V.

Scheme V



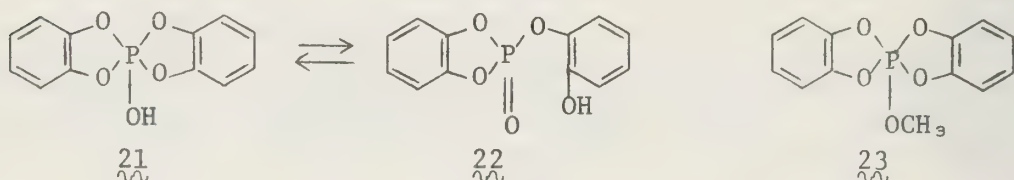
Attack of the amine by the least hindered apical approach affords 16a. Application of the principle of microscopic reversibility suggests that a leaving group exists by a pathway similar to the one followed by the entering group; therefore, apical departure is expected, but equatorial departure cannot be totally ruled out. The apical departure of the leaving group allows for 16a to collapse to 13 or 16b. Relief of ring strain may be a sufficient driving force for formation of 16b. A nucleophilic attack of 16b upon 14 would form salt 17a. Attack of the phenoxide anion with the same considerations previously postulated for apical entry and departure affords 17b which upon loss of the better apical leaving group, NR_3 , gives 15. Similarly, in Scheme VI, (2-trimethylsilyloxy)phenyl-*o*-phenylene phosphate (18) undergoes complete isomerization to spirodicatchol-(trimethylsiloxy)phosphorane (20) in aprotic solvents under amine catalysis.¹¹ The isomerization can be followed by ^{31}P and ^1H NMR spectroscopy. In the ^{31}P NMR, 18 shows the negative shift (downfield from H_3PO_4), $\delta-7.3$, characteristic of the cyclic phosphates, while 20 exhibits a chemical shift at $\delta+30.5$ (upfield from H_3PO_4), characteristic of these phosphoranes. The isomerization of 18 to 20 can be envisioned to occur via the initial formation of 19a in a fashion similar to the

Scheme VI

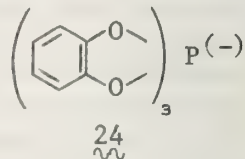


formation of 16a in Scheme V. A nucleophilic attack of the oxyanion upon the silyl group affords 19b, which may collapse to form the hexacoordinate intermediate 19c. Exit of an apical amine would afford 20. The hexacoordinate phosphorus intermediate is analogous to a compound synthesized from pyridine and a spiropentaoxyphosphorane.¹² Low temperature (-48°) ³¹P NMR studies by Ramirez and co-workers¹³ provide the first direct observation of a hydroxyphosphorane, the proposed intermediate in the basic hydrolysis of phosphate esters. The authors have identified a compound in solution which is assigned the hydroxyphosphorane structure (21) in dynamic equilibrium with the structure of hydroxyphenylphosphate (22) in the ratio of 1.5:1 as shown in Scheme VII.

Scheme VII



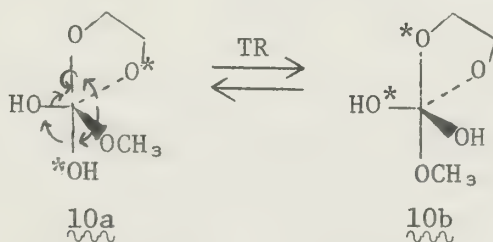
The ³¹P NMR signals characteristic of the cyclic phosphates and the spirooxyphosphoranes can be observed at low temperatures in aprotic solvents. The treatment of a solution containing 21 and 22 with diazomethane with or without the presence of boron trifluoride etherate affords exclusively the spirodicatchol methoxyphosphorane 23 whose structure was elucidated by independent synthesis. The reaction is perceived to occur via methylation of 21, but no evidence was given to rule out any mechanism involving 22 as a direct precursor of 23. X-ray crystallographic data of the phenoxy analog of 23 indicates a deviation from a trigonal bipyramidal structure, but having a structure similar to various spiropentaoxyphosphoranes.¹⁴ This may be due to steric crowding caused by the planar aromatic rings about phosphorus. The introduction of base into a solution of 21 and 22 causes the formation of the hexacoordinate anion 24, identified on the basis of ³¹P NMR.^{12,15} The formation of this anion has been postulated by Wolf and co-workers¹⁶ to occur via a series of pentacoordinate intermediates, the last of which is intramolecularly trapped. Other experiments indicating the trapping of pentacoordinate intermediates have been performed on phosphate,¹⁷ phosphonate,¹⁸ and phosphinate¹⁹ systems.



Since the evidence for the pentavalent trigonal bipyramid, 9, supports the formation of such a species as an intermediate in the hydrolysis reaction of five-membered cyclic phosphate esters as shown in Scheme III, let us now focus upon the other mechanistic considerations that can explain product formation.^{3,5-7} Since bond energy data of mono-

and dianions of various poly hydroxyphosphoranes⁹ and x-ray analysis of alkylfluorophosphoranes³ demonstrate that the oxyanion ligand prefers to occupy an equatorial position, the ring cleavage product, 3, can be rationalized on the basis of a proton transfer in 9 from the entering group, H₂O, to the ring oxygen possibly via initial proton transfer to the equatorial oxyanion to afford 11a. The protonated ring oxygen is a good leaving group in the apical position. Since the application of the principle of microscopic reversibility again suggests that the leaving group exits by a pathway similar to the one followed by the entering group, collapse of 11a would afford 3, the ring opened product. This collapse would also be predicted by basicity considerations. The protonated ring oxygen, being less basic than the equatorial ligands, would be a better leaving group. To explain the exocyclic hydrolysis product, 2, an interchange of apical and equatorial positions must be suggested to place a good leaving group in the apical position to allow for a fast exit of the least basic ligand. A proton transfer to the apical methoxyl group affords 11b, which can collapse with exit of the apical leaving group to afford 3. The interchange of the apical and equatorial groups by the mechanism of pseudorotation was first proposed by Berry²⁰ to account for the ¹⁹F NMR spectrum of PF₅. Westheimer and co-workers^{3a} have applied this pseudorotation concept to explain the hydrolysis of phosphate esters and other tetracoordinate phosphorus compounds. Pseudorotation in trigonal bipyramids is visualized by selecting an equatorial position as a pivotal point, *i.e.* the equatorial hydroxyl anion of 10a. The two apical groups are pushed away from this pivot closing the angle between them from 180° to 120°. Simultaneously, the two remaining equatorial groups are pulled toward the pivot opening the angle between them from 120° to 180°, forming a new trigonal bipyramid in which the pivotal group remains in an equatorial position, but the equatorial and apical groups have interchanged positions. An alternative formalism for the interchanging of apical and equatorial positions has been presented by Ramirez and Ugi.^{7,21} The authors envisioned a turnstile rotation mechanism corresponding to an internal rotation of one apical and one equatorial ligand rotating as a pair *vs.* the oppositely rotating trio of the remaining ligands as illustrated in Scheme VIII for the intermediate 10a. The five-membered ring would be forced to assume the role of the duo in order to minimize ring strain. Proton transfer and collapse of the pentavalent intermediate occur as described previously by Westheimer for the mechanism in Scheme III.

Scheme VIII



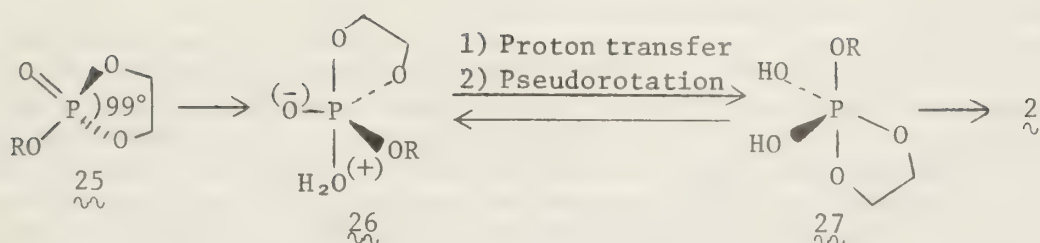
A remaining question is whether the intermediate prefers to undergo conformational transformation via a pseudorotation or a turnstile mechanism. Historically, the Berry pseudorotation mechanism has received more attention, but energy calculations utilizing CNDO/2 approximations indicate the reaction coordinates for both mechanisms are possible in simple phosphate systems.²² Results of other energy barrier calculations appear to be a function of the system and postulated underlying assumptions

of the calculations.²³ Recently, Holmes and Deiters²⁴ have presented evidence indicating that the Berry pseudorotation process is the favored mechanism for conformational permutation of the phosphate esters. The authors analyzed x-ray data for a series of cyclic phosphoranes²⁵ ranging from the trigonal bipyramidal structure to the square pyramidal one, an intermediate structural type in the Berry process. Since the pseudorotation and turnstile processes involve different reaction coordinates, analysis of structural distortions of the series of phosphoranes, approximating intermediate geometries in the conformational permutation process, from one idealized structural intermediate to the other, and measurement of the magnitude of these distortions from a defined reaction coordinate for both processes should indicate if a preference for one reaction coordinate exists. A comparison of deviations of dihedral angles about phosphorus vs. those angles of the idealized reaction coordinate for the two exchange processes indicates a strong preference for the Berry pseudorotation coordinate. However, these mechanisms of conformational interchange do not explain the dramatic rate acceleration exhibited by the five-membered cyclic phosphate esters. In order to rationalize these results, we must focus upon factors that account for fast ring opening, hydrolysis external to the ring, and the rapid oxygen exchange in the case of the five-membered cyclic diesters relative to their acyclic analogues.

The principle driving force for ring cleavage appears to be relief of ring strain. X-ray analysis and energy calculations on methyl ethylene phosphate (1) indicate an O-P-O ring bond angle of 99°, constituting a strained situation.³ Hydrolysis with ring cleavage via a less strained trigonal intermediate, 10a, having an O-P-O ring bond angle of ca. 90° may relieve such strain to predominantly account for a 5-6 kcal mol⁻¹ difference in enthalpy of hydrolysis, measured for saponification reactions of 1 and trimethyl phosphate.²⁶ Since the difference in free energy of activation, $\Delta(\Delta G^\ddagger)$, for the hydrolysis of 1 vs. trimethylphosphate is ca. 8.5 kcal mol⁻¹, and the difference in activation energies for the two compounds is ca. 7.5 kcal mol⁻¹, the thermochemical energy difference between ground states of 7.5 kcal mol⁻¹ does not totally account for the enhanced rate of 1.²⁶ Such also are the energy considerations of ethylene phosphate vs. diethylphosphate.²⁷ A facile ring opening of these five-membered cyclic phosphate esters is easily rationalized, but how does the ring structure accelerate exocyclic hydrolysis without ring opening or, in the case of the five-membered cyclic phosphate diesters, rapid oxygen exchange? The answer lies in terms of ring strain and rapid pseudorotation.

Relief of ring strain is provided by proceeding from a strained tetrahedral ground state, 25, to a trigonal bipyramidal intermediate, 26, followed by proton transfer from the entering group to the oxyanion. Effects such as ring strain, other steric strain and hydrogen bonding may allow for facile pseudorotation to afford 27 as shown in Scheme IX. This intermediate may then collapse to a product 2 similar to 2 having a lower ground state energy than that of the reactant. The considerations allow for the observed oxygen exchange in the case of phosphate diesters where the alkoxyl group is replaced by a hydroxyl group.⁴ As previously noted, the energy released in going from a strained cyclic phosphate ester to a "strain-free" trigonal bipyramid is insufficient to explain the total activation energy lowering.²⁷ Gorenstein and co-workers²⁸ attribute at least some of the energy difference to stereoelectronic effects in the trigonal bipyramid-like transition state or intermediate.

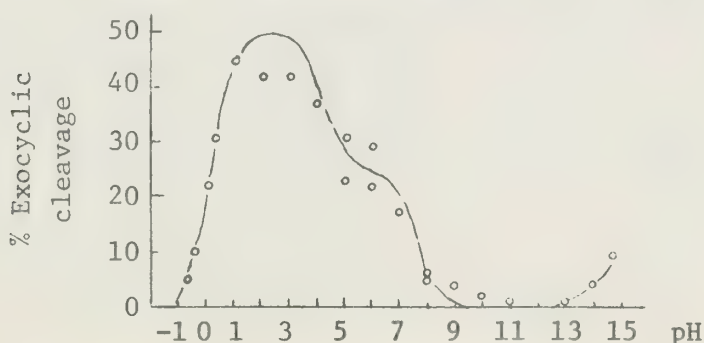
Scheme IX



Molecular orbital calculations on the conformational isomers of the various postulated transition states were performed. In tetracoordinate phosphorus species, the dependence of overlap populations on conformation about ester bonds is derived from an "anomeric effect",²⁹ i.e. the interaction of a trans antiperiplanar oxygen lone pair with the antibonding orbital on an adjacent bond, resulting in a strengthening of the oxygen bond bearing the apical lone pair and a weakening of the bond adjacent to the one with the lone pair. Calculations applying this anomeric effect indicate that the lowest energy conformational state for the transition state in the acyclic case is sterically inaccessible, but in the acyclic case, the lowest energy transitional state conformer is accessible; thus, a higher energy of activation is suggested for the acyclic phosphate esters. The calculations performed by the authors allow for a qualitative explanation for the total activation energy lowering of five-membered cyclic *vs.* acyclic phosphate esters. In a recent communication, Brauman *et al.*³⁰ present evidence indicating that the rapid rate of exocyclic cleavage for the hydrolysis of five-membered phosphate esters is an intrinsic property of the phosphate system and not a function of solvation. Gas phase studies of P^{\sim} and trimethyl phosphate using the trapped ion, pulsed ICR technique³¹ with OH^- as the nucleophile indicate a more rapid appearance of methoxide for P^{\sim} than for trimethyl phosphate. Under the conditions of the experiment, no ring opened product was observed. Ring opening would lead to a vibrationally excited ion-molecule adduct which would probably not live long enough to be collisionally stabilized at low pressures. Similar to the liquid phase, no rate enhancement was observed for the phosphinates, P^{\sim} . The data presented can be easily explained by the solution mechanistic considerations previously presented, thus giving strong support for this proposed mechanism.

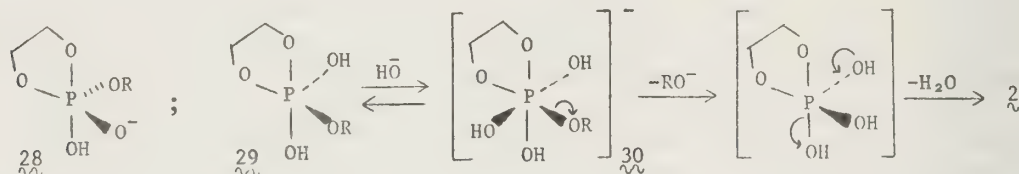
Since the Westheimer mechanism accounts for enhanced rates of the five-membered cyclic phosphate esters, the pH-product profile shown in Figure 1 should be analyzed in terms of mechanistic considerations.^{7c, 32}

Figure 1. pH-Product profile for the hydrolysis of methyl ethylene phosphate in water at 25°C



This dependence of product distribution upon pH may be rationalized as a function of rates of pseudorotation, proton transfer, and ring opening. In the pH region of high exocyclic cleavage (Figure 1), the acidity of the system is such that proton transfer from the entering group, H_2O , to the equatorial oxyanion as noted in Scheme III is fast, giving a neutral species which may rapidly undergo pseudorotation to afford an intermediate similar to 10b in Scheme III. This intermediate can collapse to the exocyclic cleavage product, 2. In this pH region, proton transfer to afford a neutral species for rapid pseudorotation is faster than proton transfer to or protonation of the cyclic oxygen to afford ring opening. In a region of $pH \leq 3$, the percent of exocyclic cleavage product decreases markedly to essentially zero as a direct function of pH. In this region, rate of proton transfer to an oxyanion is decreased and the decomposition of a cationic intermediate similar to 11a exceeds the rate of pseudorotation necessary to account for exocyclic cleavage. In moderately alkaline solutions, pseudorotation in accord with previous considerations is retarded due to the formation of an intermediate, 28. Proton transfer does not afford a neutral species to undergo rapid pseudorotation necessary for exocyclic cleavage; thus, ring opening predominates. In strong alkali, exocyclic cleavage reappears. Experimentally, the hydrolysis of 1 is second-order in hydroxide ion.³³ In view of kinetic studies pertaining to the hydrolysis of pentaaryloxyphosphoranes³⁴ and the second-order behavior of the hydroxide ion, the cleavage results are best explained in terms of an extended Westheimer mechanism as shown in Scheme X.

Scheme X



This mechanism involves the addition of a second hydroxide ion to the pentacoordinate intermediate, 29, to form a hexacoordinate intermediate, 30. A stepwise loss of ligands with the best leaving group exiting first would afford product 2.

The mechanism presented for the hydrolysis of five-membered cyclic phosphate esters is applicable to other cyclic tetracoordinate phosphorus systems, permitting a consistent mechanistic treatment throughout this area of phosphorus chemistry. The experimental and energetic considerations presented permit strong justification for this hydrolytic mechanism.

BIBLIOGRAPHY

1. A. D. Toy, "Phosphorus Chemistry in Everyday Living", Am. Chem. Soc., Washington, D.C., 1976.
2. F. Covitz and F. H. Westheimer, J. Am. Chem. Soc., 85, 1773 (1963).
3. (a) F. H. Westheimer, Accts. Chem. Res., 1, 70 (1968); (b) J. R. Cox, Jr. and O. B. Ramsay, Chem. Rev., 64, 317 (1964).
4. P. C. Haake and F. H. Westheimer, J. Am. Chem. Soc., 83, 1102 (1961).
5. W. K. Hamer, J. Chem. Soc., Sect. C, 404 (1966).
6. D. A. Usher, E. A. Dennis, and F. H. Westheimer, J. Am. Chem. Soc., 87, 2320 (1965).
7. (a) F. Ramirez, S. Pfohl, E. A. Tsolis, J. F. Pilot, C. P. Smith, I. Ugi, D. Marquarding, P. Gillespie, and P. Hoffmann, Phosphorus, 1, 1

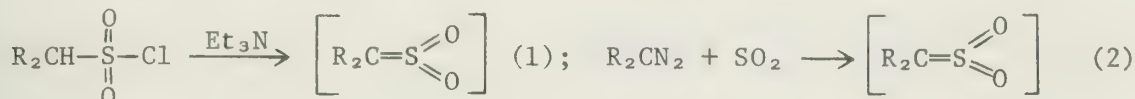
- (1971); (b) I. Ugi and F. Ramirez, *Chem. in Britain*, 8, 198 (1972); (c) P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem., Int. Ed. Engl.*, 12, 91 (1973).
8. P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 10, 687 (1971).
9. (a) W. E. McEwen and K. D. Berlin, ed., "Organophosphorus Stereochemistry", Vol. II, Dowden, Hutchinson, and Ross, Stroudsburg, Pa. (1975); (b) R. R. Holmes, *J. Am. Chem. Soc.*, 96, 4143 (1974).
10. F. Ramirez, *Accts. Chem. Res.*, 1, 168 (1968).
11. F. Ramirez, M. Nowakowski, and J. F. Marecek, *J. Am. Chem. Soc.*, 98, 4332 (1976).
12. F. Ramirez, V. A. V. Prasad, and J. F. Marecek, *J. Am. Chem. Soc.*, 96, 7269 (1974).
13. F. Ramirez, M. Nowakowski, and J. F. Marecek, *J. Am. Chem. Soc.*, 99, 4515 (1977).
14. (a) F. Ramirez, A. J. Bigler, and C. P. Smith, *J. Am. Chem. Soc.*, 90, 3507 (1968); (b) R. Sarma, F. Ramirez, and J. F. Marecek, *J. Org. Chem.*, 41, 473 (1976).
15. H. R. Alicock and E. C. Bissell, *J. Am. Chem. Soc.*, 96, 7269 (1974).
16. A. Munoz, M. Gallagher, A. Klabe, and R. Wolf, *Tetrahedron Lett.*, 673 (1976).
17. T. Koizumi, Y. Watanabe, Y. Yoshida, and E. Yoshii, *Tetrahedron Lett.*, 1705 (1974).
18. B. A. Arbusov, A. O. Vizel, K. M. Ivanovskaya, and E. O. Gold'fard, *J. Gen. Chem. (USSR)*, 45, 1204 (1975).
19. G. Kemp and S. Trippett, *Tetrahedron Lett.*, 4381 (1976).
20. R. S. Berry, *J. Chem. Phys.*, 32, 933 (1960).
21. I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie, and F. Ramirez, *Accts. Chem. Res.*, 4, 288 (1971).
22. C. S. Cheung, R. A. Beaudet, and G. A. Segal, *J. Am. Chem. Soc.*, 92, 4158 (1970).
23. (a) J. A. Pople, *Accts. Chem. Res.*, 3, 217 (1970); (b) H. H. Jaffe, *ibid.*, 2, 136 (1969).
24. R. R. Holmes and J. A. Deiters, *J. Am. Chem. Soc.*, 99, 3318 (1977).
25. (a) R. K. Brown and R. R. Holmes, *J. Am. Chem. Soc.*, 99, 3326 (1977); (b) J. R. Devillers and R. R. Holmes, *ibid.*, 99, (1977); (c) P. F. Meunier, J. A. Deiters, and R. R. Holmes, *Inorg. Chem.*, 15, 2572 (1976).
26. E. T. Kaiser, M. Panar, and F. H. Westheimer, *J. Am. Chem. Soc.*, 85, 602 (1963).
27. J. A. Gelt, F. H. Westheimer, and J. M. Sturtevant, *J. Biol. Chem.*, 250, 5059 (1975).
28. D. G. Gorenstein, B. A. Luxon, J. B. Findlay, and R. Momii, *J. Am. Chem. Soc.*, 99, 4170 (1977).
29. (a) J. M. Lehn and G. Wipff, *J. Chem. Soc., Chem. Commun.*, 800 (1975); (b) L. Radom, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, 94, 2371 (1972); (c) S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffman, *ibid.*, 95, 3806 (1973).
30. O. I. Asubiojo, J. I. Brauman, and R. H. Levin, *J. Am. Chem. Soc.*, 99, 7707 (1977).
31. R. T. McIver, Jr., and R. C. Dunbar, *Int. J. Mass Spectrom. Ion. Phys.*, 7, 471 (1971).
32. C. H. Bamford and C. F. Tipper, ed., "Comprehensive Chemical Kinetics", Vol. 10, Elsevier, Amsterdam (1972).
33. R. Kluger, F. Covitz, E. A. Dennis, L. D. Williams, and F. H. Westheimer, *J. Am. Chem. Soc.*, 91, 6066 (1969).
34. W. C. Archie and F. H. Westheimer, *J. Am. Chem. Soc.*, 95, 5955 (1973).

THE FORMATION AND CHEMISTRY OF SULFENES

Reported by William Y. Lam

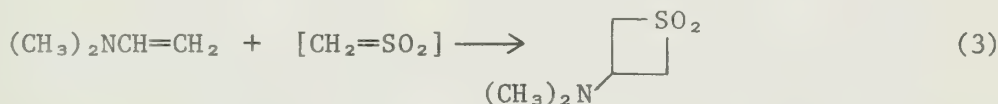
December 12, 1977

Sulfenes,¹ the sulfonyl analogues of ketenes, are molecules of the formula $R_2C=SO_2$. They are known only as reactive intermediates. No stable monomeric sulfene has yet been isolated.¹ In the absence of addend, dimer² or polymer³ has been obtained. Two common routes to generate sulfenes are treatment of alkanesulfonic acid derivatives with base (Eq. 1)⁴ and reaction of diazoalkanes and sulfur dioxide (Eq. 2).⁵

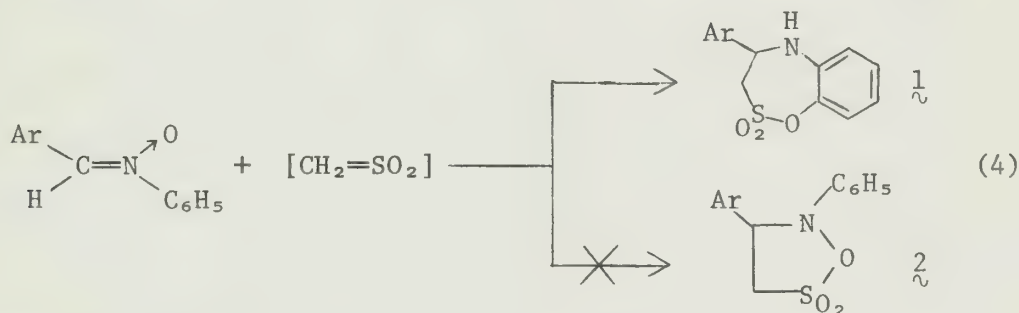


Sulfene formation by thermolysis of alkyl vinyl sulfones⁶ and thiete 1,1-dioxides,⁷ and photolysis of cyclic unsaturated sultones⁸ and 3-thietanone 1,1-dioxide⁹ have been reported, but these reactions are not of general applicability. Verification of treatment transient sulfene derives from product analysis,^{1,10} rate studies,¹¹ and from flash vacuum pyrolysis generation of the parent followed by trapping at -196° .¹² The IR spectrum, however, is the only physical property of sulfene as yet measured directly.

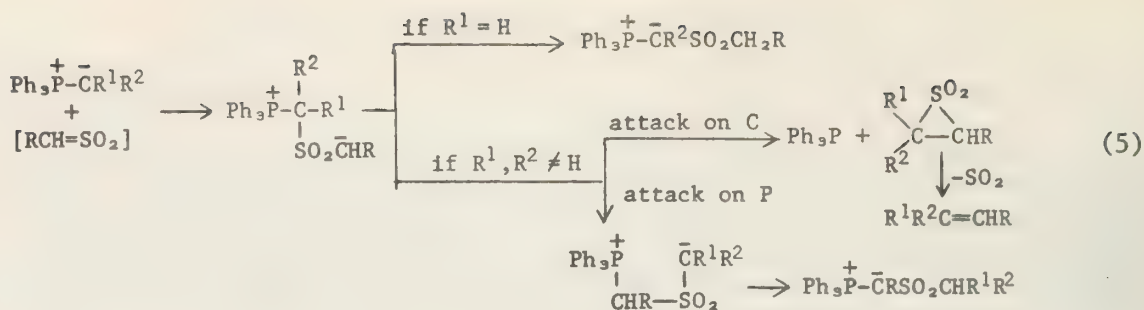
The most generally useful reaction of sulfenes is the sulfonylation of active hydrogen compounds¹³ such as alcohols, amines, and mercaptans. When an alkanesulfonyl chloride is treated with triethylamine in the presence of electron-rich olefins such as enamines (Eq. 3), ketene acetals and amins, cycloaddition of the sulfene intermediate to the olefin results, and thietane 1,1-dioxide generally is formed.^{4,14}



Ynamines have been found to react similarly with sulfenes under comparable conditions to give the thiete 1,1-dioxides.¹⁵ Formation of β -sultones has been found to be general with many perhalogenated carbonyl compounds.¹⁶ Various diaryl nitrones form 1:1 adducts with sulfenes, which are established to be $\frac{1}{2}$ instead of $\frac{2}{2}$ expected from 1,3-cycloaddition (Eq. 4).¹⁷



Phosphorus ylides react with sulfenes¹⁸ to give episulfones or olefins, and the (alkanesulfonyl) methylene phosphorus ylides. However, with α -hydrogen bearing P-ylides, α -sulfonylated phosphorus ylides are obtained (Eq. 5).



Reaction of diazoalkanes with sulfenes generated from sulfonyl halides and triethylamine may lead to a variety of unsymmetrical episulfones,¹⁹ which can further decompose to give alkenes and sulfur dioxide.

BIBLIOGRAPHY

1. For a review on sulfenes: J. F. King, *Acc. Chem. Res.*, **8**, 10 (1975).
2. G. Opitz and H. R. Mohl, *Angew. Chem. Int. Ed. Engl.*, **8**, 73 (1969).
3. (a) L. A. Pagrette, J. P. Freeman, and R. W. Houser, *J. Org. Chem.*, **34**, 2901 (1969); (b) J. F. King, P. de Mayo, and D. L. Verdun, *Can. J. Chem.*, **47**, 4509 (1969).
4. W. E. Truce and L. K. Liu, *Mech. React. Sulfur Compd.*, **4**, 145 (1969).
5. T. Nagai and N. Tokura, *Int. J. Sulfur Chem.*, **7**, 207 (1972).
6. J. F. King and D. R. K. Harding, *J. Am. Chem. Soc.*, **98**, 3312 (1976).
7. D. C. Dittmer, J. E. McCaskie, J. E. Babiarz, and M. V. Ruggeri, *J. Org. Chem.*, **42**, 1910 (1977) and references cited therein.
8. J. F. King, E. G. Lewars, D. R. K. Harding, and R. M. Enanoza, *Can. J. Chem.*, **53**, 3656 (1975).
9. R. F. T. Langendries and F. C. DeSchryver, *Tetrahedron Lett.*, 4781 (1972).
10. (a) W. E. Truce and R. W. Campbell, *J. Am. Chem. Soc.*, **88**, 3599 (1966); (b) J. F. King and T. Durst, *ibid.*, **87**, 5684 (1965).
11. J. F. King and T. W. S. Lee, *J. Am. Chem. Soc.*, **91**, 6524 (1969).
12. (a) J. F. King, R. A. Marty, P. de Mayo, and D. L. Verdun, *J. Am. Chem. Soc.*, **93**, 6304 (1971); (b) R. Langendries, F. C. DeSchryver, P. de Mayo, R. A. Marty, and J. Schutyser, *ibid.*, **96**, 2964 (1974).
13. (a) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970); (b) R. K. Crossland, W. E. Wells, and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **93**, 4217 (1971); (c) D. S. Noyce, B. E. Johnston, and B. Weinstein, *J. Org. Chem.*, **34**, 463 (1969); (d) H. Bohme and P. H. Meyer, *Synthesis*, 205 (1971).
14. (a) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes", Academic Press, New York, N.Y., 1967; (b) L. A. Paquette and J. P. Freeman, *J. Am. Chem. Soc.*, **91**, 7548 (1969); (c) P. L. F. Chang and D. C. Dittmer, *J. Org. Chem.*, **34**, 2791 (1969); (d) W. E. Truce, D. J. Abraham, and P. Son., *ibid.*, **32**, 990 (1967); (e) F. S. Abbott, J. E. Coates, and K. Haya, *ibid.*, **42**, 3502 (1977).
15. (a) D. R. Eckroth and G. M. Love, *J. Org. Chem.*, **34**, 1136 (1969); (b) M. H. Rosen, *Tetrahedron Lett.*, 647 (1969).
16. W. E. Truce and K. Liu, *Tetrahedron Lett.*, 517 (1970).
17. W. E. Truce, J. R. Norell, R. W. Campbell, and D. G. Brady, *J. Org. Chem.*, **34**, 3097 (1969).
18. Y. Ito, M. Okano, and R. Oda, *Tetrahedron*, **23**, 2137 (1967).
19. N. M. Fischer, *Synthesis*, 393 (1970).

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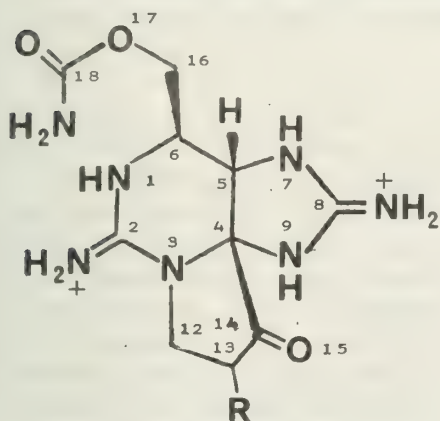
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SAXITOXIN

Reported by Robert Foster

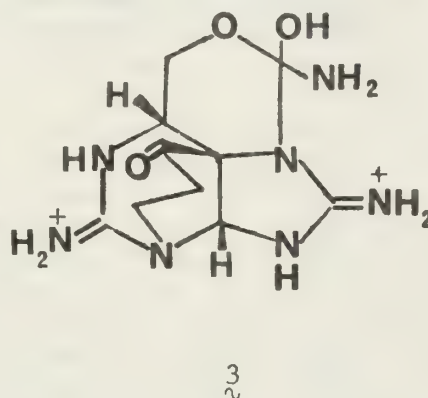
January 23, 1978

Saxitoxin (1), named for the Alaska butter clam (Saxidomus giganteus) in which it has been found, is one of the most toxic non-peptide substances known,¹ with a toxicity of nearly 5,000 MU/mg,^{2,3} or 10 µg/Kg. It is known



1, R = H Saxitoxin

2, R = OH Gonyautoxin



to be the cause of the paralytic shellfish poisoning which coincides with West Coast dinoflagellate blooms⁴ (red tides) in temperate waters. These blooms (or sudden population increases) result in the accumulation and concentration of the toxin in mollusks such as Mytilus californianus and S. giganteus which eat these algae and in massive fish kills when fish consume these algae. The shellfish, although themselves not poisoned, become poisonous and pose a health hazard to coastal inhabitants.⁵ The connection between the algae and the toxicity of the mollusks was proven in 1966⁵ when an identical toxin was isolated from M. californianus, S. giganteus, and axenic cultures of the dinoflagellate Gonyaulax catenella. The link between algae and shellfish is not completely understood, however.⁶ Recently,^{3,7} red tides and paralytic shellfish poisoning on the East Coast have been linked to another species of Gonyaulax, G. tamarensis, that produces a closely analogous toxin (2)⁸ which is concentrated in the shellfish Mya arenaria and has been isolated from axenic cultures of G. tamerensis.

Saxitoxin acts by selectively blocking the entrance to sodium channels in neuron membranes, and thereby preventing the transient Na⁺ ion conductance increases associated with action potentials. It is thought that an acid group at the sodium channel entrance^{9,10} must be ionized for sodium ions to pass,¹⁰ and that in this ionized form, the acid can bind saxitoxin reversibly.¹¹ The presence of saxitoxin seems to have no effect on K⁺¹² or Cl⁻⁹ ion currents, or on transmitter (acetylcholine) release.¹³ Saxitoxin is less active at high pH,¹⁰ and its binding to the sodium channel mouth is inhibited by H⁺, Ca⁺⁺, and Tl⁺ ions.¹¹ Amidine and guanidinium analogs of saxitoxin have been used in nerve preparations; they too block the action potential.

Saxitoxin dihydrochloride is a white, amorphous hygroscopic solid¹⁴ found as the ketone hydrate, which dehydrates only under vigorous conditions.¹⁵ It has two pKa's which have not been entirely explained--one at 8.24 and one at 11.60.¹⁴ When saxitoxin is placed in 50% aqueous ethanol, its lower pKa increases to 9.05¹⁶--behavior which is characteristic of ionizable O-H, not N-H.¹⁷ The presently accepted structure (1)^{14,15} shows no such ionizable O-H (when the ketone is reduced to an alcohol, the pKa data are the same¹⁴) and one is forced to accept the pKa's as being those of the two guanidinium groups.^{6,14} Saxitoxin is moderately acid stable, but decomposes rapidly in alkaline media.¹⁸ Peroxide treatment in alkali yields a fluorescent product which is useful in sensitive quantitative assays of saxitoxin.^{19,10}

The structure that was first reported²¹ is incorrect in two aspects (3)^{14,16}--a cyclol form of the carbamoyl moiety, and an N(3)-C(5) bridge instead of an N(3)-C(4) bridge. The new structure was established in 1975 by two independent X-ray structure determinations. Crystals of the p-bromobenzenesulfonate¹⁵ and ethyl hemiketal¹⁴ saxitoxins (respectively) confirmed the basic trialkyl tetrahydropurine structure. Saxitoxin lacks internal hydrogen bonds. The X-ray structure determination establishes that the C-ring bridges between N(3) and C(4) and that the carbamoyl group is in the open chain form (¹³C NMR also shows this).¹⁴ Two factors led to the first postulated structure. The cyclol was proposed to explain the change in pKa in aqueous ethanol (vide supra). Secondly, the true structure may have been discounted because of (a) expected larger vicinal coupling between the protons of C(5) and C(6), and (b) an expected greater chemical shift for the C(5) proton. The downfield resonance of the C(5) proton is now explained as spatial deshielding by the hydrate oxygens, and the C(5)-C(6) proton coupling, originally interpreted as long-range coupling between the protons of C(4) and C(6), is thought to be so low due to a dihedral angle of 89°.¹⁴

A stereospecific synthesis of saxitoxin has now been reported.¹ In it, the C-ring is formed first, then the A- and finally the B-ring. Two interesting features of the synthesis are a sulfide elimination to form a functionalized precursor to the A,C-ring system,²² and the use of chlorosulfonyl isocyanate to attach the carbamoyl moiety. Formation of the B-ring has been the subject of a separate paper.²³

The better understanding of saxitoxin serves a number of goals. In physiology, this molecule is an excellent tool for the study of synaptic and neuromuscular transmissions. It can be used to separate ion currents by selective blocking (i.e. Na⁺ from K⁺). It can be a valuable tool in the study of drug action; the fact that the availability of saxitoxin has been a limitation to its employment makes the recent synthesis all the more timely. The continued interest in neurophysiology and pharmacology, as well as natural occurrences of paralytic shellfish poisoning, makes the study of saxitoxin interesting and worthwhile.

BIBLIOGRAPHY

1. H. Tanino, T. Nakata, T. Kaneko, and Y. Kishi, J. Am. Chem. Soc., 99, 2818 (1977).
2. One mouse unit (MU) is defined as an amount to kill a 20-g mouse within 15 min: H. Sommer and K. F. Meyer, Arch. Pathol., 24, 560 (1937).

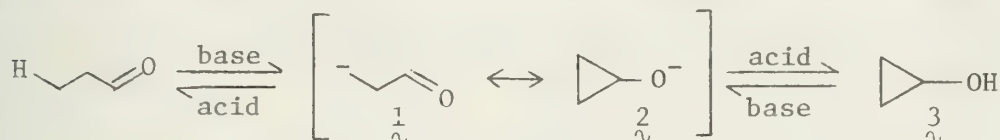
3. V. E. Ghazarossian, E. J. Shantz, H. K. Schnoes, and F. M. Strong, *Biochem. Biophys. Res. Commun.*, 59, 1219 (1974).
4. See also Proceedings of the First International Conference on Toxic Dinoflagellate Blooms (1975).
5. E. J. Shantz, J. M. Lynch, G. Vayvada, K. Matsumoto, and H. Rapoport, *Biochemistry*, 5, 1191 (1966).
6. P. J. Scheuer, *Accts. Chem. Res.*, 10, 33 (1977).
7. Y. Shimizu, M. Alam, Y. Oshima, and W. E. Fallon, *Biochem. Biophys. Res. Commun.*, 66, 731 (1975).
8. Y. Shimizu, L. J. Buckley, M. Alam, Y. Oshima, W. E. Fallon, H. Kasai, I. Miura, V. P. Gullo, and K. Nakanishi, *J. Am. Chem. Soc.*, 98, 5414 (1976).
9. P. B. Goldberg and C. Y. Kao, *J. Pharmacol. Exp. Ther.*, 186, 569 (1973).
10. B. Hille, *Fed. Prod.*, 34, 1318 (1975).
11. R. Henderson, J. M. Ritchie, and G. R. Strichartz, *J. Physiol. (London)*, 235, 783 (1973).
12. T. Narahashi, *Fed. Proc.*, 31, 1124 (1972).
13. T. Narahashi, *Phys. Rev.*, 54, 813 (1974).
14. J. Bordner, W. E. Thiessen, H. A. Bates, and H. Rapoport, *J. Am. Chem. Soc.*, 97, 6008 (1975).
15. E. J. Shantz, V. E. Ghazarossian, H. K. Schnoes, F. M. Strong, J. P. Springer, J. O. Pezzanite, and J. Clardy, *J. Am. Chem. Soc.*, 97, 1238 (1975).
16. J. L. Wong, R. Oesterlin, and H. Rapoport, *J. Am. Chem. Soc.*, 93, 7344 (1971).
17. E. Grunwald and B. J. Berkowitz, *J. Am. Chem. Soc.*, 73, 4939 (1951); B. Gutbezahl and E. Grunwald, *J. Am. Chem. Soc.*, 75, 559 (1953).
18. The Merck Index, Ed. 9, Merck and Co., Rahway, N. J., 1976, p. 1086.
19. L. J. Buckley, M. Ikawa, and J. J. Sasner, Jr., *J. Agr. Food Chem.*, 24, 107 (1976).
20. H. A. Bates and H. Rapoport, *J. Agr. Food Chem.*, 23, 237 (1975).
21. J. L. Wong, M. S. Brown, K. Matsumoto, R. Oesterlin, and H. Rapoport, *J. Am. Chem. Soc.*, 93, 4633 (1971).
22. M. Roth, P. Dubs, E. Götschi, and A. Eschenmoser, *Helv. Chim. Acta*, 54, 710 (1971).
23. H. Taguchi, H. Yazawa, J. F. Arnett, and Y. Kishi, *Tetrahedron Lett.*, 627 (1977).

HOMOENOLATE ANIONS AND THEIR SYNTHETIC EQUIVALENTS

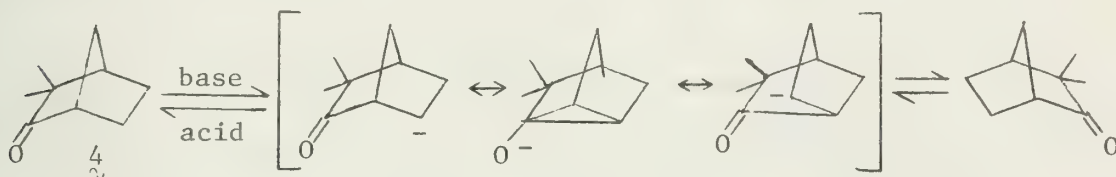
Reported by Dennis Stack

January 26, 1978

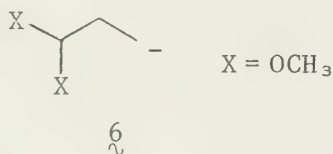
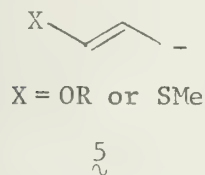
The term homoconjugation refers to the stabilization of either positive or negative charges by orbital overlap with a π -electron system through noncontiguous atoms. Homoenolate anions, therefore, arise from this concept. Structures 1 and 2 represent the simplest homoenolate anions and structure 3, cyclopropanol, represents the simplest homoenol.¹



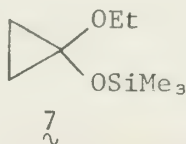
The concept of homoenolization was not recognized until 1962 when Nickon and co-workers demonstrated its existence in their study of the racemization of optically active camphenilone, 4, with base at elevated temperatures.^{2a-d} After the initial reports by the Nickon group, other instances of this phenomenon and even synthetic applications began to appear in the literature.^{3a,b}



The development of an homoenolate anion as a synthetic tool, however, has only been recently explored. Synthetic equivalents to anion 1 which have been developed fall into four classes. Structure 5 represents one



class.^{4a-h} With this type of anion, however, reactions at the α -position become a serious drawback. Structure 6 generalizes a second class of synthons for 1.^{5a,b} One such synthetic equivalent for 6 was used by Büchi and Wüest^{5a} in their synthesis of (\pm)-nuciferal, while Kondo and Tunemoto have demonstrated the usefulness of their homoenolate equivalent in the preparation of prostaglandin precursors.^{5b} The third class has but one member, 7, which is an ester homoenolate anion equivalent and reacts with aldehydes and aromatic acetals to yield lactones and esters, respectively.⁶ The final category is based on a two-step approach in which the last step requires an oxidation to attain the carbonyl moiety.^{7a,b}



BIBLIOGRAPHY

1. For a recent review on cyclopropanol chemistry, see D. H. Gibson and C. H. DePuy, *Chem. Rev.*, 74, 605 (1974).
2. (a) A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, 84, 4604 (1962); (b) A. Nickon, J. H. Hammons, J. L. Lambert, and R. O. Williams, *ibid.*, 85, 3713 (1963); (c) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *ibid.*, 87, 1615 (1965); (d) A. Nickon and J. L. Lambert, *ibid.*, 88, 1905 (1966).
3. (a) A. Nickon, J. L. Lambert, J. E. Oliver, D. F. Covey, and J. Morgan, *J. Am. Chem. Soc.*, 98, 2593 (1976), and references cited therein; (b) B. M. Trost and L. H. Latimer, *J. Org. Chem.*, 42, 3212 (1977).
4. (a) E. J. Corey and D. E. Cane, *J. Org. Chem.*, 35, 3405 (1970); (b) K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, 95, 7926 (1973) and *Bull. Chem. Soc. Jpn.*, 48, 1567 (1975); (c) H. Ahlbrecht and G. Rauchswalbe, *Synthesis*, 417 (1973); (d) H. W. Thompson and B. S. Huegi, *J. Chem. Soc., Chem. Commun.*, 636 (1973); (e) G. Sturtz, B. Corbel, and H. Normant, *C. R. Acad. Sci., Ser. C*, 277, 395 (1973); (f) D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, 96, 5560 (1974); (g) W. C. Still and T. L. Macdonald, *ibid.*, 96, 5561 (1974); (h) K.-H. Giess, B. Seuring, R. Pieter, and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 13, 479 (1974).
5. (a) G. Buchi and H. Wuest, *J. Org. Chem.*, 34, 1122 (1969); (b) K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1397 (1975).
6. E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 99, 7360 (1977).
7. (a) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, 37, 1947 (1972); (b) B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 95, 5321 (1973).

STEREOSPECIFIC CYCLOBUTANONE SYNTHESIS

Reported by Paul Adams

January 30, 1978

Following the observation by Trost¹ in 1970 that quenching of the reaction of cyclopropyllithium and triphenylsulfonium fluoroborate with cyclohexanone produced spiro[5.3]nonan-2-one, the importance of substituted cyclobutanones in organic synthesis has increased steadily. Cyclobutanones can be prepared by a variety of methods,² most of which lack stereospecificity. The ability to generate cyclobutanones stereospecifically from the ubiquitous carbonyl function is important for geminal alkylation and spiroalkylation - two techniques to be discussed which have been employed with success recently in the stereocontrolled synthesis of natural products.

I. Two Stereospecific Routes to Cyclobutanones: The Ability to Generate Complementary Stereochemistry

Treatment of aldehydes and ketones with diphenylsulfonium cyclopropylide produces oxaspiropentanes, **1**, in high isolated yields. The latter compounds, when allowed to react with lithium salts possessing a non-nucleophilic anion in refluxing benzene, afford cyclobutanones in excellent yields^{3,13} (Scheme I, Table 1).

Scheme I

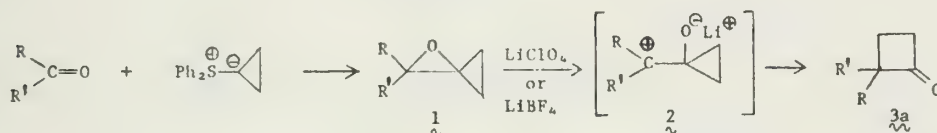


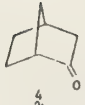

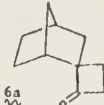
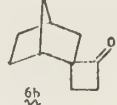


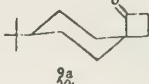

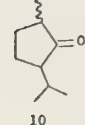
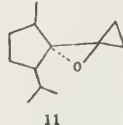
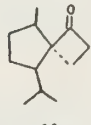
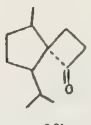
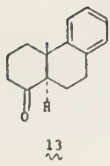
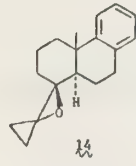
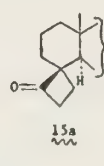
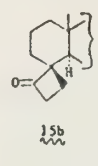

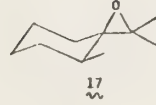

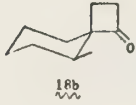
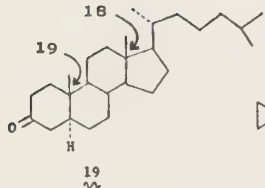
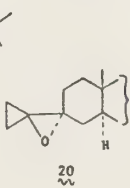
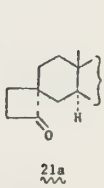
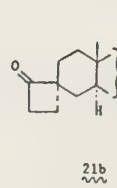
Table 1. Cyclobutanone Synthesis Employing Scheme 1

<u>Aldehyde or Ketone</u>	<u>Cyclobutanone</u>	<u>% Yield^a</u>
		86
		87
		92
		94
		97
		91

^aOverall isolated yield from starting carbonyl compound.

Since attack of the sulfur ylide proceeds on the sterically less hindered face of the ketone, the new carbon-carbonyl carbon bond of the cyclobutanone is introduced on the sterically more hindered face of the starting ketone (see examples in Table 2). An α -oxycyclopropylcarbinyl cation 2, has been invoked³ as an intermediate in the oxaspiropentane rearrangement. Stereospecificity observed in Table 2 is thus attributed to the rapidity of rearrangement compared to other processes such as bond rotation.

Table 2. Stereospecific Cyclobutanone Synthesis Employing Schemes I and II.

<u>Ketone</u>	<u>Oxaspiropentane</u>	<u>Scheme</u>	<u>Cyclobutanones</u>		<u>% Yield^a</u>	<u>% a:b</u>
		I			92	82:18
		I			95	91:9
		I			88	100:0
		I			78	100:0
"	"	II	"	"	68	36:64
		I			80	100:0
"	"	II	"	"	85	13:87
		I			51	100:0
"	"	II	"	"	62	2:98

^aOverall isolated yield of cyclobutanone from starting ketone.

Very recently,⁴ Trost has developed an alternate conversion of $1 \rightarrow 3$ employing selenoxide as a leaving group (Scheme II). The key feature of this approach is the ability to generate cyclobutanones stereospecifically and opposite in stereochemistry from that obtained by Scheme I (see Table 2).

Scheme II

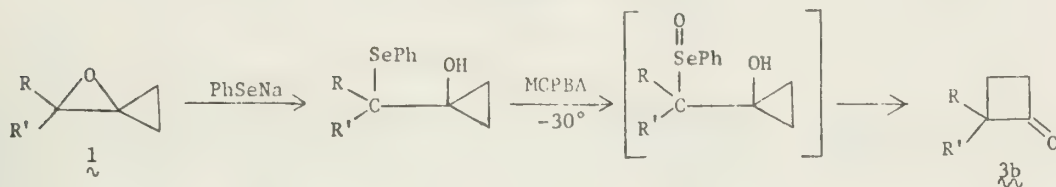
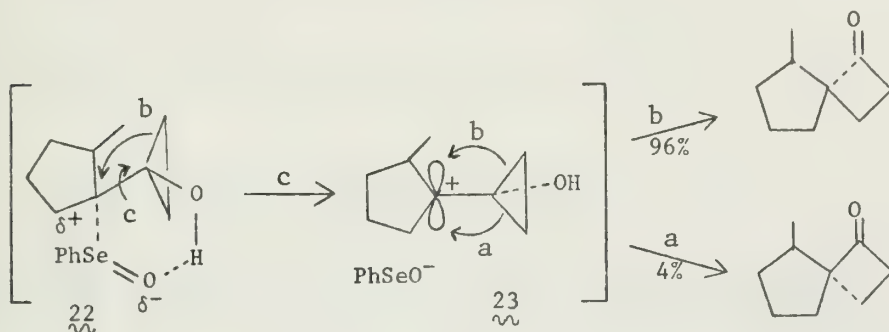
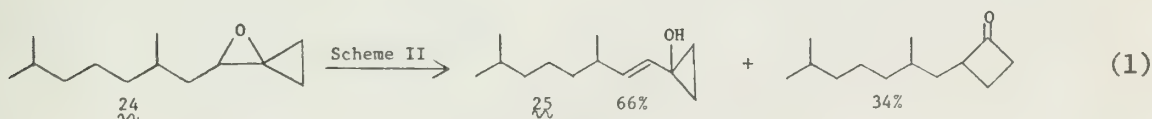


Figure 1 illustrates a proposed⁴ mechanistic rationale of selenoxide eliminations to give cyclobutanones derived from 2-methylcyclopentanone. A benzeneselenate tight ion pair, 22 , which can undergo back-side migration (arrow b) has been proposed as a transition state to account for the reverse stereochemistry of the major products obtained via Scheme II. Alternatively, 22 can convert to conformationally relaxed ion pair 23 which is capable of axial (arrow b) or equatorial (arrow a) migration of a cyclopropyl bond to form a cyclobutanone.

Figure 1



Indeed, the results of Table 2 show the high degree of stereocontrol for the formation of either cyclobutanone from a single oxaspiropentane precursor. However, the approach based on selenium appears to be limited to ketones only, in that oxaspiropentane 24 , obtained from the corresponding aldehyde, affords vinylcyclopropanol 25 as the major product of the rearrangement (Eq. 1).⁴



II. Stereochemical Assignment of Cyclobutanones

Proton NMR benzene-induced solvent shifts have played a useful role in assigning stereochemistry of cyclobutanone products. The methyl group of cyclobutanone $15a$ in Table 2 shows a downfield shift of 0.11 ppm in

benzene versus deuteriochloroform, while the methyl in 15b is observed to shift 0.16 ppm upfield.⁴ These observations are in accord with what is expected based on work by Williams and Bhacca.⁵ An upfield shift is observed for a methyl group if behind the plane perpendicular to and bisecting the C-O bond of the carbonyl group, while a downfield shift is observed for a methyl group in front of the plane. A similar effect is observed for the C(19) methyl of 21a and 21b. The C(18) methyl of these steroid derivatives, however, shows very little induced solvent shift, as predicted by the fact that it is about on the zero shift plane.

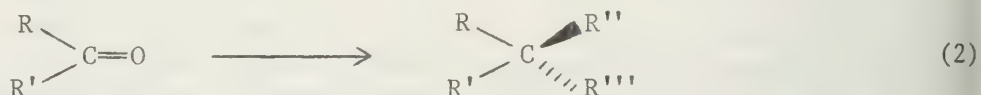
Lanthanide induced shifts help confirm the stereochemistry of 12a.⁶ The three methyl doublets at 1.00, 0.97, and 0.87 ppm shift to 1.42, 1.27, and 1.13 ppm, respectively, in the presence of Eu(thd)₃. A syn relationship of the methyl and isopropyl substituents to the carbonyl group is implied by the magnitude of these shifts, along with a 0.60 ppm shift of the methylene group α to the carbonyl.

¹³C NMR spectral data aid in confirming the configurations of 18a and 18b.⁴ 1,3-diaxial steric compression of the 3-methylene carbon in 18b results in a 4.5 ppm upfield shift compared with the corresponding resonance in 18a. Unfortunately, resonances of the carbonyl carbons (which are far removed from other resonances in each spectrum) in Table 2 do not fit into a regular pattern.

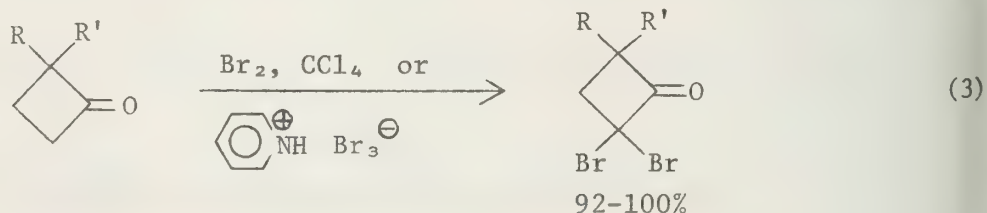
Optical rotary dispersion is valuable for assignments of cyclobutanones which are derived from optically active starting materials (e.g., 21a and 21b).^{4,7} Finally, a longer gas chromatographic retention time is seen for the "b-series" cyclobutanones of Table 2 on polar columns, in accordance with the lower steric congestion of the carbonyl group.

III. Synthetically Useful Transformations of Cyclobutanones

A. Geminal Alkylation. Cyclobutanones present a facile route for converting a carbonyl compound to a quaternary center with controlled stereochemistry as depicted in Eq. 2. The key to this transformation

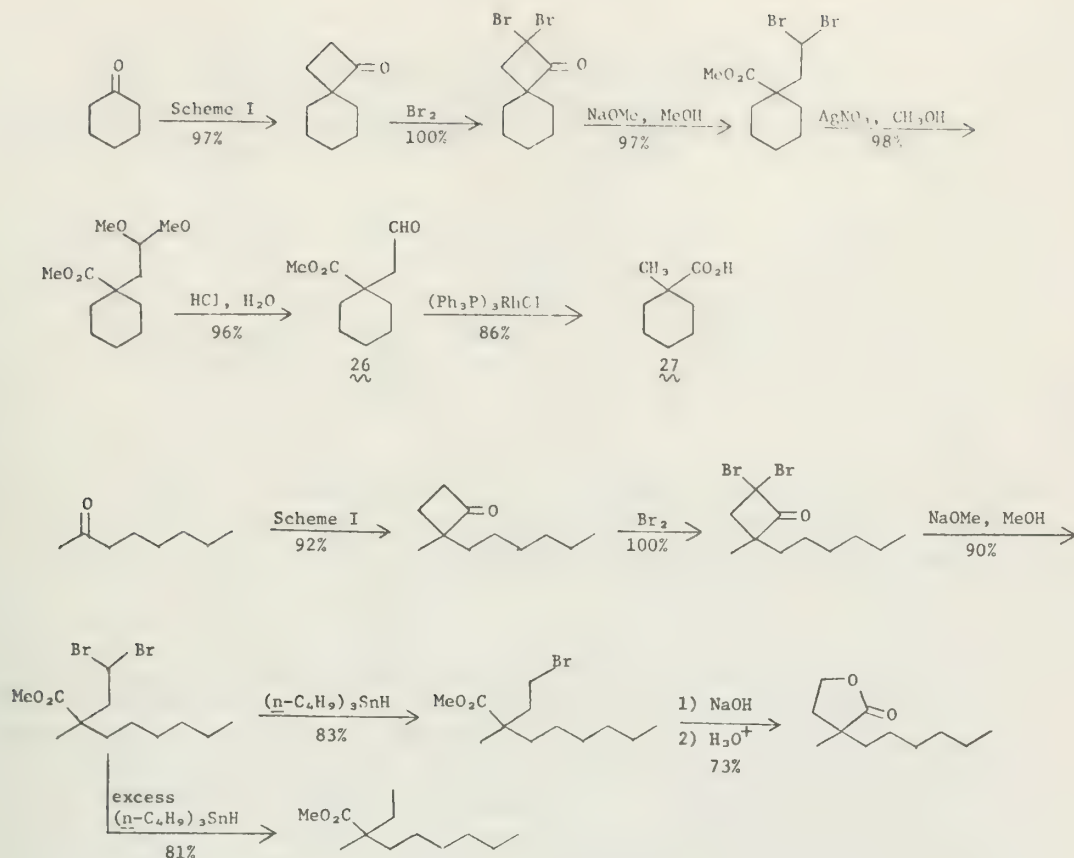


is the ability to alpha-dibrominate cyclobutanones in excellent yield (Eq. 3).⁸ Molecular bromine in carbon tetrachloride or pyridinium bromide perbromide in acetic acid⁹ effect the conversion quantitatively,



or nearly so. The resulting dibromocyclobutanones, upon cleavage with methanolic sodium methoxide, serve as a means of modifying the substituents introduced in the geminal alkylation procedure. Scheme III describes reactions that have been carried out using cyclohexanone and 2-octanone as starting ketones.⁸ Although some of the transformations

Scheme III



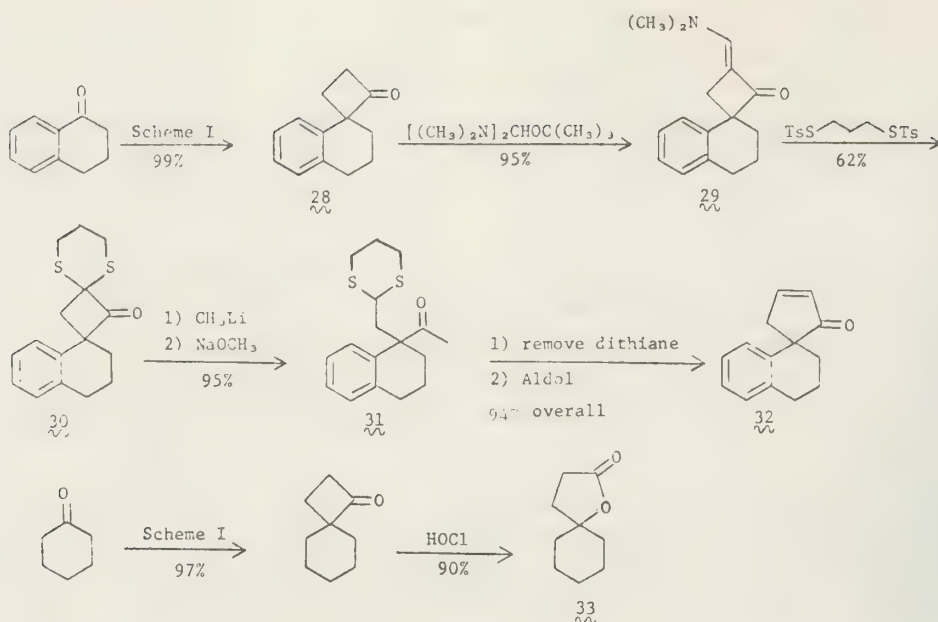
represent five- or six-step sequences, many of the individual reactions proceed rapidly and in excellent yield, and the overall yield is high. The ability to generate an α -methyl carboxylic acid unit (**27**) from a carbonyl group is noteworthy, as the former structural unit is common to a number of natural products.¹⁰ Decarbonylation of aldehyde **26** using Wilkinson's catalyst¹¹ completes the approach to this unit for cyclohexanone. A minor drawback of the methodology described in Scheme III is the inability to use starting materials which possess functionality sensitive to molecular bromine. Although an example will be described elsewhere in this review, it follows that if cyclobutanone annelation is stereospecific, the overall process of geminal alkylation will also be stereospecific.

B. Spiroannellation. The conversion represented by Eq. 4, whereby the carbonyl carbon of the starting ketone is converted to a spiro ring junction, has been termed spiroannellation. Two general approaches are



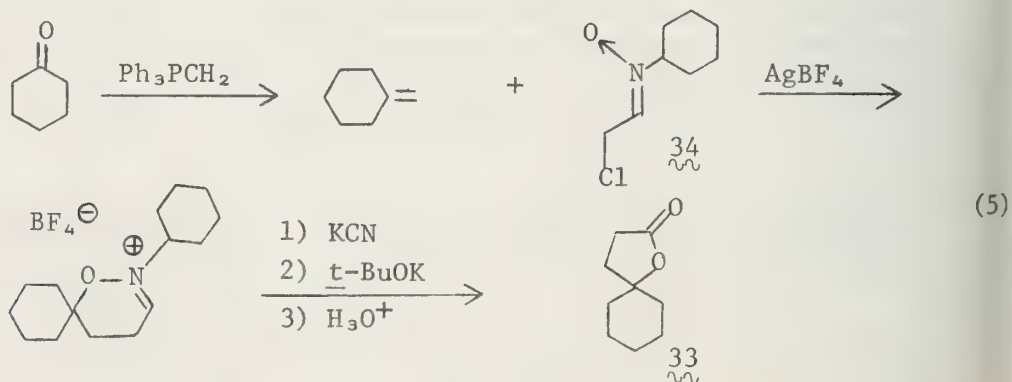
available for introducing the ring that is added as a cyclopentenone¹² or γ -lactone moiety.^{3,13}

Scheme IV

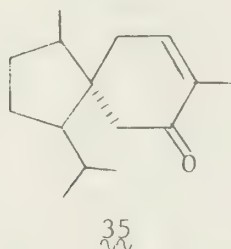


Scheme IV describes the elaboration of tetralone to spiro-cyclopentenone **32** employing dithiane chemistry.¹² A necessary requirement for introduction of the dithiane unit is the activation of the α -methylene carbon of **28** by conversion to the vinylogous amide **29**. Tert-butoxybis-(dimethylamino)methane¹⁴ accomplishes the desired activation by condensing with cyclobutanone **28** to afford **29** in 95% yield. Once the dithiane unit has been introduced using 1,3-trimethylenedithiotosylate,¹⁵ cleavage of the cyclobutanone with methyl lithium followed by treatment with sodium methoxide affords functionalized ketone **31**. Standard dithiane removal and aldolization complete the approach in high yield.

The conversion of cyclohexanone to spiro- γ -butyrolactone **33**^{3,13} takes advantage of the ease with which cyclobutanones undergo the Baeyer-Villiger oxidation.¹⁶ A major driving force for the reaction is the release of approximately 27 kcal/mole of strain energy upon opening a four-membered ring. Thus, basic hydrogen peroxide or hypochlorous acid effect the conversion in typical yields of 80-100%.¹³ This spiro-lactone synthesis compares quite favorably in yield with an alternate state of the art pathway developed by Eschenmoser and co-workers¹⁷ utilizing chloronitrone **34** (Eq. 5). An overall yield of less than 20% was achieved by the route outlined in Eq. 5 compared to 88% for that in Scheme IV.

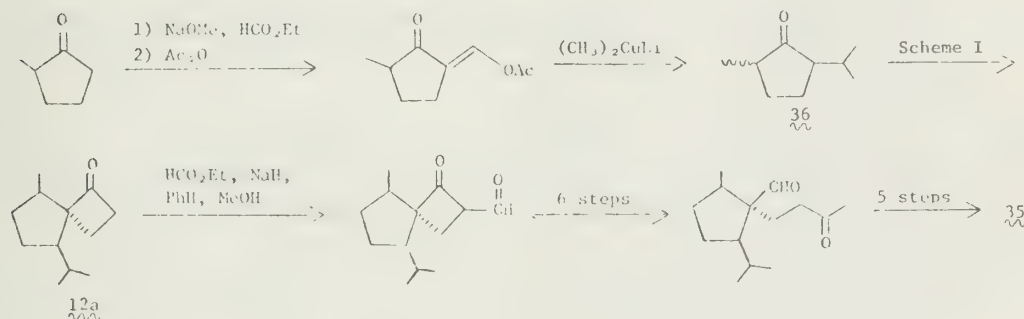


IV. Stereocontrolled Cyclobutanone Formation in
Natural Product Synthesis: The Total
Synthesis of Acorenone B.



Sesquiterpenes possessing the spiro[4.5]decane system are of considerable interest as biosynthetic intermediates in terpene biogenesis, constituents of essential oils, antifungal agents, and stress metabolites.¹⁸ A subset of this class of sesquiterpenes, the acoranes, have been the objective of a considerable amount of synthetic work.¹⁹ Scheme V outlines, in part, the pathway undertaken by Trost and co-workers⁶ to acorenone B, 35, the first stereocontrolled synthesis of this sesquiterpene.

Scheme V. Stereocontrolled Approach to Acorenone B



The key to the approach involves generation of stereohomogeneous cyclobutanone 12a, which was cleaved to form two chains of different functionality at the spiro carbon (geminal alkylation). An interesting feature of the synthesis is that an isomeric mixture of ketone 36 afforded cyclobutanone 12a with 100% stereospecificity (see also Table 2). It happens that interconversion of the E and Z isomers of 36 is faster than ylide addition to the carbonyl group. Thus, the Z isomer, possessing the most sterically unhindered face, reacts selectively with the sulfur ylide, to give stereohomogeneous oxaspiropentane 11. Rearrangement of 11 in the presence of lithium fluoroborate afforded exclusively cyclobutanone 12a, as described earlier.

Thus, the stereochemistry of the spiro carbon, introduced at a very early stage in the synthesis, is maintained throughout in the subsequent steps to acorenone B.

In conclusion, two distinct pathways exist for preparing cyclobutanones from oxaspiropentanes with controlled stereochemistry. Configurations of the products obtained can be assigned on the basis of solvent and

lanthanide-induced proton NMR shifts, ^{13}C NMR, ORD, and GLC elution orders. The applications of cyclobutanones in organic synthesis based on geminal and spiroalkylation are of interest to the synthetic chemist when faced with the problem of constructing a quaternary center in a molecule.

BIBLIOGRAPHY

1. B. M. Trost, R. W. LaRoche, and M. J. Bogdanowicz, *Tetrahedron Lett.*, 3449 (1970).
2. See for example: J. D. Roberts and C. W. Sauer, *J. Am. Chem. Soc.*, 71, 3925 (1949); C. S. Marvel and M. I. Kohan, *J. Org. Chem.*, 16, 741 (1951); J. Marchand-Brynaert and L. Ghosez, *J. Am. Chem. Soc.*, 94, 2870 (1972); E. Wenkert and D. P. Strike, *J. Org. Chem.*, 27, 1883 (1962); O. L. Chapman, D. J. Pasto, and A. A. Grisworld, *J. Am. Chem. Soc.*, 84, 1213, 1220 (1962); A. B. Smith, A. M. Foster, and W. C. Agosta, *ibid.*, 94, 5100 (1972); J. D. Roberts, G. B. Kline, and H. E. Simmons, *ibid.*, 75, 4765 (1953); J. R. Salaun and J. M. Conia, *Tetrahedron Lett.*, 2849 (1972); N. J. Turro and R. B. Gagosian, *J. Am. Chem. Soc.*, 92, 2036 (1970).
3. B. M. Trost, *Acc. Chem. Res.*, 7, 85 (1974).
4. B. M. Trost and P. H. Scudder, *J. Am. Chem. Soc.*, 99, 7601 (1977).
5. D. H. Williams and N. S. Bhacca, *Tetrahedron*, 21, 1641, 2021 (1965).
6. B. M. Trost, K. Hiroi, N. Holy, *J. Am. Chem. Soc.*, 97, 5873 (1975).
7. R. Damman, M. Braun, and D. Seebach, *Helv. Chim. Acta*, 59, 2821 (1976).
8. B. M. Trost, M. J. Bogdanowicz, and J. Kern, *J. Am. Chem. Soc.*, 97, 2218 (1975); B. M. Trost and M. J. Bogdanowicz, *ibid.*, 95, 2038 (1973).
9. C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, 70, 417 (1948).
10. See for example: F. Giarrusso and R. E. Ireland, *J. Org. Chem.*, 33, 3560 (1968); M. E. Kuehne and J. A. Nelson, *ibid.*, 35, 161 (1970); S. C. Welch and C. P. Hagan, *Syn. Commun.*, 2, 221 (1972) and 3, 29 (1973).
11. J. Tsuji and K. Ohno, *J. Am. Chem. Soc.*, 90, 94 (1968); H. M. Walborsky and L. E. Allen, *ibid.*, 93, 5465 (1971); W. D. Stohrer and R. Hoffmann, *ibid.*, 94, 779 (1972); R. E. Pincock, J. Schmidt, W. B. Scott, and E. J. Torupka, *Can. J. Chem.*, 50, 3958 (1972).
12. B. M. Trost and M. Preckel, *J. Am. Chem. Soc.*, 95, 7862 (1973); B. M. Trost, M. Preckel, and L. M. Leichter, *ibid.*, 97, 2224 (1975).
13. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 95, 5321 (1973).
14. J. Gutzwiller, G. Pizzolato, and M. Uskokovic, *J. Am. Chem. Soc.*, 93, 5907 (1971); H. Brederick, F. Efrenberger, and G. Simchen, *Chem. Ber.*, 101, 41 (1968), and references therein.
15. R. B. Woodward, I. J. Pachter, and M. L. Scheinbaum, *J. Org. Chem.*, 36, 1137 (1971).
16. For reviews, see: C. H. Hassall, *Organic Reactions*, 9, 73 (1957); H. O. House, *Modern Synthetic Reactions*, W. A. Benjamin, New York, N. Y., 1972, pp. 306-7, 321-8.
17. T. K. Gupta, D. Felix, U. M. Kemp, and A. Eschenmoser, *Helv. Chim. Acta*, 55, 2198 (1972).
18. For a review, see J. A. Marshall, S. F. Brady, and N. H. Anderson, *Fortschr. Chem. Org. Naturst.*, 31, 283 (1974); J. B. Stothers and E. W. Ward, *J. Chem. Soc., Chem. Commun.*, 75 (1975); D. T. Coxon, K. R. Price, B. Howard, S. F. Osman, E. B. Kalan, and R. M. Zacharius, *Tetrahedron Lett.*, 2921 (1974); D. T. Coxon, R. F. Curtis, K. R. Price, and B. Howard, *ibid.*, 2363 (1974).

19. For synthetic work in the acoranes, see: W. Oppolzer, *Helv. Chim. Acta*, 56, 1812 (1973); G. Guest, C. R. Hughes, R. Ramage, and A. Sattar, *J. Chem. Soc., Chem. Commun.*, 526 (1973); J. N. Marx and R. L. Norman, *Tetrahedron Lett.*, 4375 (1973); J. M. Conia, J. P. Drouet, and J. Gore, *Tetrahedron*, 27, 248 (1971); H. Wolf and M. Kolleck, *Tetrahedron Lett.*, 451 (1975); D. A. McCrae and L. Dolby, *J. Org. Chem.*, 42, 1607 (1977); J. N. Marx and L. R. Norman, *J. Org. Chem.*, 40, 1602 (1975).

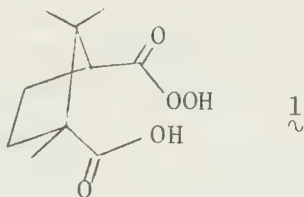
THE SYNTHESIS OF OPTICALLY ACTIVE EPOXIDES VIA CHIRAL OXYGEN- OR METHYLENE- TRANSFER REAGENTS

Reported by Garret D. Figuly

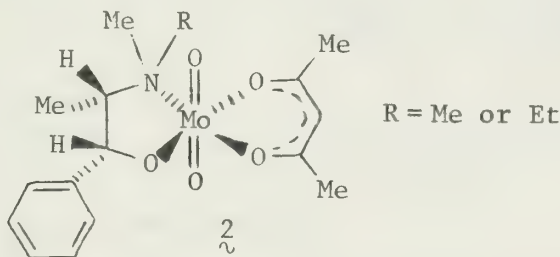
February 2, 1978

The importance of the epoxide function in metabolic processes¹ has led many investigators to attempt to synthesize optically active epoxides. While enzymes can synthesize chiral epoxides quite readily,² chemists have had little success in attempts at synthesizing optically active epoxides using monoperoxycamphoric acid (MPCA) and other peroxy acids³ (normal enantiomeric excesses (ee) are 2-4%).

By way of improvement, Pirkle and Rinaldi have now found that when MPCA is purified to give only one isomer (1), optical yields of the chiral epoxides produced are increased 50 - 100% over yields previously reported (ee of up to 9 - 10%).⁴



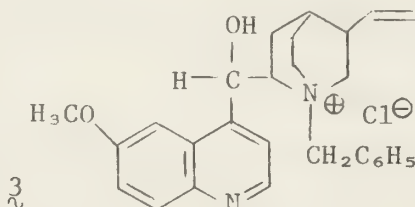
Recently, methods for the formation of asymmetric epoxides have been developed which introduce chirality through reagents other than optically active peroxy acids. For example, Sharpless and his co-workers have found that allylic alcohols can undergo asymmetric epoxidations when such transition metals as vanadium⁵ and molybdenum^{5,6} with chiral ligands are employed as catalysts. Thus far, the best enantiomeric excess using these catalysts is 50% when α -phenylcinnamyl alcohol is epoxidized using a vanadium catalyst with N-phenylcamphorhydroxamic acid as a chiral ligand and tert-butyl hydroperoxide as the oxidizing agent.⁵ Yamada and his co-workers have also found independently that allylic alcohols can undergo asymmetric epoxidations through the use of chiral chelating complexes (2) as catalysts to give enantiomeric excesses of up to 33%.⁷



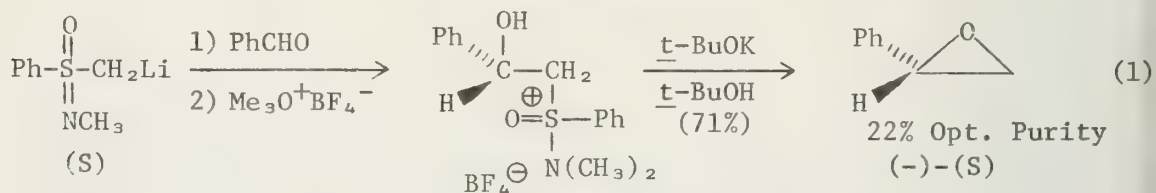
Epoxidations using Sharpless' catalysts in the presence of ¹⁸O-enriched water may provide evidence that the intact alkyl hydroperoxide is present in the activated complex responsible for oxygen transfer to the olefin.⁸ These experiments would limit the mechanistic proposals acceptable for these epoxidations.

Novel methods of synthesizing optically active epoxides have recently been reported by the research groups of Wynberg and Hiyama. Using the quaternary quinine salt 3 as a chiral phase-transfer catalyst with

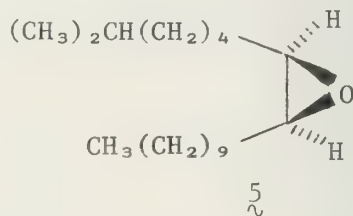
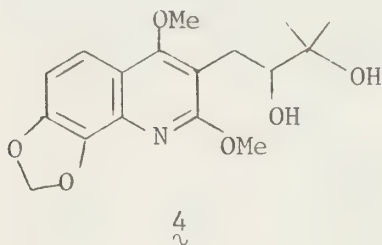
aqueous hydrogen peroxide or *t*-butyl hydroperoxide as an oxidizing agent, Wynberg reports enantiomeric excesses of up to 25% when he uses such electron-poor olefins as quinones or chalcones.⁹ Hiyama has used β -oxido quaternary ammonium zwitterions as chiral phase-transfer catalysts to synthesize optically active oxiranes from aldehydes.¹⁰



A method of synthesizing optically active epoxides via methylene transfer has been developed by Johnson and co-workers. Optical purities as high as 22% have been reported when optically active sulfoximinium ylides are used to produce asymmetric epoxides (Eq. 1).¹¹⁻¹⁵



Other work in the area of asymmetric epoxidations has included the use of some of the above epoxidation methods in the synthesis of such natural products as orixine (4)¹⁶ and disparlure (5),¹⁷ and in the development of new methods for the resolution of optically active epoxides.^{18,19}



BIBLIOGRAPHY

1. A few of the more recent articles cover: (a) cyclization of squalene: E. E. van Tamelen, J. D. Willett, and R. B. Clayton, *J. Am. Chem. Soc.*, **89**, 3371 (1967); (b) arene oxides: D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974); (c) quinone epoxides: M. R. Demuth, P. E. Garrett, and J. D. White, *J. Am. Chem. Soc.*, **98**, 634 (1976); (d) terpene epoxides: D. J. Goldsmith, *J. Am. Chem. Soc.*, **84**, 3913 (1962); and (e) a nitrogenous metabolite: Y. S. Mohammed and M. Luckner, *Tetrahedron Lett.*, 1953 (1963).
2. See (a) H. Hikino, C. Konno, T. Nagashima, T. Kohama, and T. Takemoto, *Chem. Pharm. Bull.*, **25**, 6 (1977), and (b) S. W. May, M. S. Steltenkamp, R. D. Schwartz, and C. J. Moody, *J. Am. Chem. Soc.*, **98**, 7856 (1976) for two examples.

3. For reviews on these early methods see: (a) D. R. Boyd and M. A. McKervey, *Quart. Rev. (London)*, 22, 95 (1968); (b) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", American Chemical Society, Washington, D.C., 1976, pp. 258-262; (c) G. Berti in "Topics in Stereochemistry", eds. N. L. Allinger and E. L. Eliel, Interscience, N.Y., 1973, Vol. 7, p. 93, and references therein.
4. W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, 42, 2080 (1977).
5. R. C. Michaelson, R. E. Palermo, and K. B. Sharpless, *J. Am. Chem. Soc.*, 99, 1990 (1977).
6. R. C. Michaelson, Ph.D. Thesis, Massachusetts Institute of Technology, Jan., 1976.
7. S. Yamada, T. Mashiko, and S. Terashima, *J. Am. Chem. Soc.*, 99, 1988 (1977).
8. A. O. Chong and K. B. Sharpless, *J. Org. Chem.*, 42, 1587 (1977). For another mechanistic approach see: R. Curci, F. DiFuria, and G. Modena, *J. Chem. Soc. Perkin II*, 576 (1977). For examples of other mechanisms see: M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, 35, 1839 (1970), and E. S. Gould, R. R. Hiatt, and K. C. Irwin, *J. Am. Chem. Soc.*, 90, 4573 (1968).
9. R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, and H. Wynberg, *Tetrahedron Lett.*, 1831 (1976).
10. T. Hiyama, T. Mishima, H. Sawada, H. Nozaki, *J. Am. Chem. Soc.*, 97, 1626 (1975). Note that some of the results in this paper have been withdrawn. For the withdrawal see: T. Hiyama, T. Mishima, H. Sawada, and H. Nozaki, *J. Am. Chem. Soc.*, 98, 641 (1976).
11. C. R. Johnson, R. A. Kirchhoff, and H. G. Corkins, *J. Org. Chem.*, 39, 2458 (1974).
12. C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, 95, 7418 (1973).
13. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, 95, 7692 (1973).
14. C. R. Johnson in "Twenty-Fourth National Organic Chemistry Symposium of the American Chemical Society", Auspices of the Division of Organic Chemistry and Colorado State University, June 22-26, 1975, pp. 163-174.
15. C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *J. Am. Chem. Soc.*, 95, 7424 (1973).
16. R. M. Bowman and M. F. Grundon, *J. Chem. Soc. (C)*, 2368 (1967).
17. D. G. Farnum, T. Veysoglu, A. M. Cardé, B. Duhl-Emswiler, T. A. Pancoast, T. J. Reitz, and R. T. Cardé, *Tetrahedron Lett.*, 4009 (1977).
18. M. N. Akhtar and D. R. Boyd, *J. Chem. Soc., Chem. Commun.*, 916 (1975).
19. P. L. Rinaldi, 13th A. C. S. Midwest Regional Meeting, Rolla, MO., Abstract No. 518, Nov. 3 and 4, 1977; and personal communication from P. L. Rinaldi.

SYNTHESIS OF CARBON-11, NITROGEN-13, AND OXYGEN-15 RADIOPHARMACEUTICALS

Reported by Michael R. Kilbourn

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The use of the positron-emitting isotopes of carbon (^{11}C), nitrogen (^{13}N), and oxygen (^{15}O) in the synthesis of radiopharmaceuticals has only recently been investigated. The use of these radionuclides allows for isotopic labelling of (theoretically) any organic molecule, as opposed to the more widespread, but less appealing, non-isotopic labelling using isotopes of such elements as iodine, bromine, indium, tellurium, technetium, and others.¹

Carbon-11, nitrogen-13, and oxygen-15 are all short-lived radionuclides that decay by positron (β^+) emission; their *in vivo* usage is based on the visualization of the two 511 KeV gamma annihilation photons emitted per decay event.^{2,3} The short half-life of these radionuclides requires ready access to a cyclotron or linear accelerator, rapid synthesis, and quick delivery of the finished product to the site of use.

^{11}C -Labelled Compounds. Carbon-11 has a half-life of only 20.4 minutes, as compared with a half-life of 5,720 years for carbon-14.⁴ This short-lived isotope of carbon can be prepared by a variety of nuclear reactions, but those most widely used are the $^{10}\text{B}(\text{d},\text{n})^{11}\text{C}$, $^{11}\text{B}(\text{p},\text{n})^{11}\text{C}$, $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ reactions.²

Nearly one hundred carbon-11 compounds have been prepared to date (Table 1). The availability of acetylene, carbon dioxide, hydrogen cyanide, formaldehyde, and methyl iodide in carbon-11 labelled form has allowed for the introduction of the radionuclide as one- or two-carbon fragments. Typical rapid reactions used for the introduction of carbon-11 are (1) S_2N displacement of halides by $^{11}\text{CN}^-$, (2) reaction of Grignard or lithium reagents with $^{11}\text{CO}_2$, (3) methylation with ^{11}C -methyl iodide or

Table 1. ^{11}C -Labelled Radiopharmaceuticals and Intermediates

Compound	Chemical Yield %	Radiochemical Yield % ^a	Synthesis Time (min)	Reference
methyl iodide				13
formaldehyde				13
acetylene				14
methanol			5-10	15
ethanol			10-60	16
isopropyl alcohol			10-60	15
glycerol			75	17
mannitol	16		75	17
hexadecanol			55	18
aliphatic and aromatic acids (26 acids)		40-98	40	19
acetoacetic acid		52-55	40	12
nicotinic acid		60-85	25	10
urocanic acid	45			20
glycine				20,21

Table 1 (cont'd)

Compound	Chemical Yield %	Radiochemical Yield % ^a	Synthesis Time (min)	Reference
β-alanine	35	4.5	90	22
aspartic acid	29			18
methionine				11,21
(±)-α-phenylglycine	45	6	40	22,23,24
(±)-α-phenylalanine		1	70	22,23,24
tryptophan	10-20	22		25
amino acids (general- by recoil labelling)				5
proteins	35-43	35		26,27
aliphatic amines (C ₄ -C ₈)		20-40		28
N-methyl-1,4-diamino- butane			15	2
dopamine·HCl	10-15	52	65	7
		30	60	9
norepinephrine·HCl	10-15	10	40	6,30
iododopamine			60	29
polyamines				31
clomipramine	80		35	32
hexamethonium				33
DOPA	25-35	18-32		34
α-N-alkylamino- phenylacetoneitriles	6-53	11-65	49-82	35
α-N-arylaminoaryl- acetoneitriles	20-66	19-61	35-75	35
glucose-fructose (mixture)		6	45-50	36
glucose				37
galactose			75	38
dialkylhydantoins	11-50	7-36	70-90	40,41
diarylhydantoins	37-61	24-60	71-83	40-41
alkylarylhydantoins		11-36	106	40,41
spirohydantoins	30-81	41-60	73-81	40-41
p-hydroxyphenyl- phenylhydantoin				
p-hydroxyphenyl- phenylhydantoin		40-58	70	41
thymidine	77	5	110	42
albumin	70	38		43
fibrinogen		33		43

Table 1 (cont'd)

Compound	Chemical Yield %	Radiochemical Yield % ^a	Synthesis Time (min)	Reference
blood cells			10	45,46,47
acetyl phosphate		20-35	10	48
chlorpromazine		10-20	30	49
1-aminocyclopentane- carboxylic acid				50
1-aminocyclobutane- carboxylic acid				51
17 α -ethynyl estradiol				8

^aYields may or may not be corrected for decay

¹¹C formaldehyde, (4) addition of ¹¹CN⁻ to carbonyl compounds (cyanohydrin formation), (5) addition of ¹¹CO₂ to carbanions derived from isonitriles and carbonyl compounds, and (6) addition of labelled lithium acetylide to a carbonyl compound. Examples of these reactions are shown in Figure 1.

Figure 1. Exemplary syntheses of ¹¹C-labelled compounds

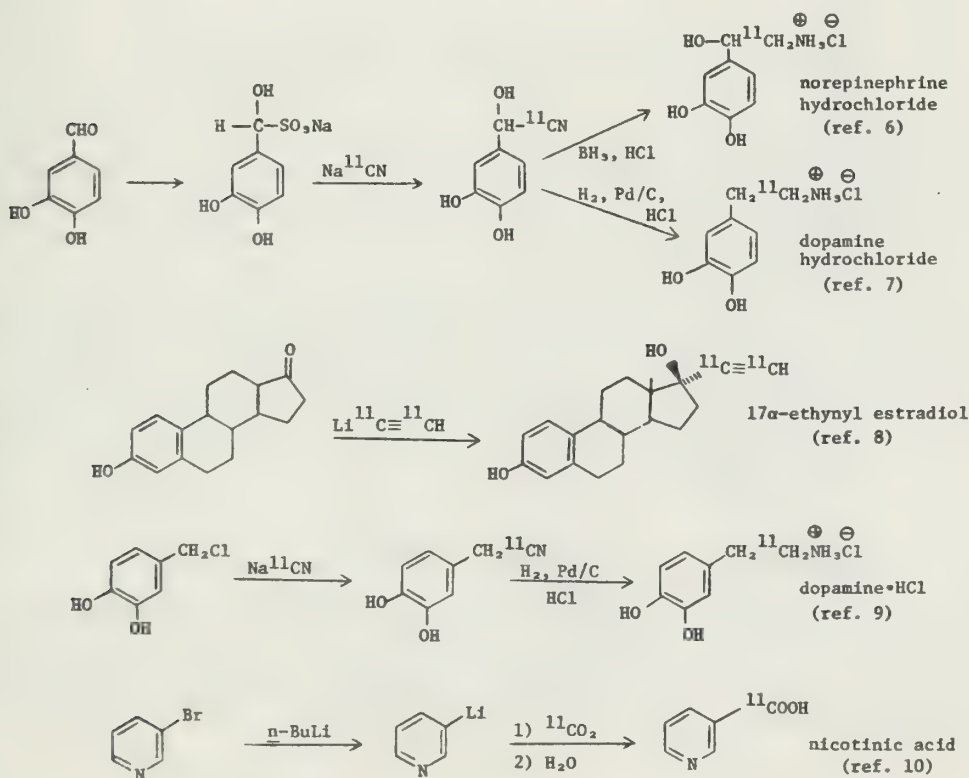
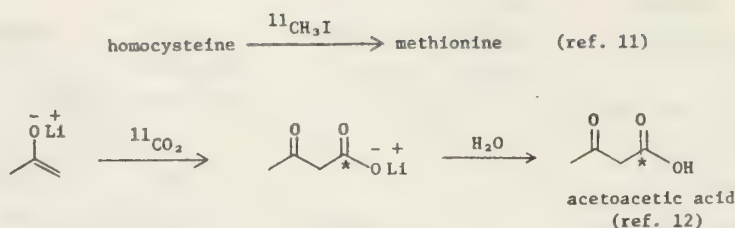


Figure 1 (cont'd)



The synthesis of ^{11}C -labelled compounds has also been accomplished by recoil labelling (bombardment of unlabelled material with ^{11}C atoms).⁵ This approach has yielded labelled amino acids, but the products are usually heterogeneous and not yet suitable for in vivo usage.

^{13}N -Labelled Compounds. This radionuclide of nitrogen, nitrogen-13, has a half-life of only 9.96 minutes. For production, the nuclear reactions $^{12}\text{C}(\text{d},\text{n})^{13}\text{N}$ and $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ are commonly employed.³

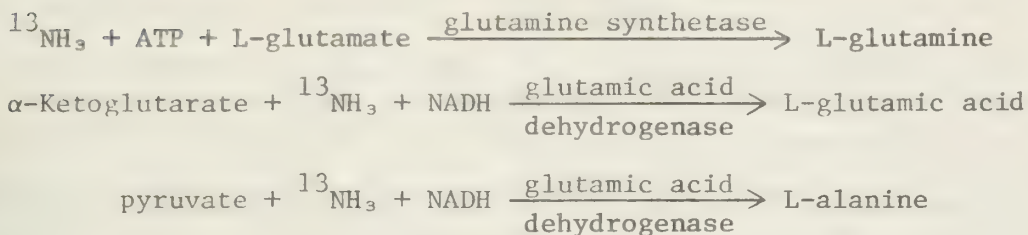
Few ^{13}N -labelled compounds have been prepared. The gases ^{13}NN and $^{13}\text{NH}_3$ have been prepared and used in in vivo studies. Labelled ammonia has additionally served as a substrate for numerous enzymatic reactions to produce ^{13}N -labelled amino acids (Table 2). These enzymatic reactions

Table 2. ^{13}N -Labelled Radiopharmaceuticals and Intermediates

Compound	Chemical Yield %	Radiochemical Yield %	Synthesis Time (min)	Reference
^{13}NN				52
$^{13}\text{NH}_3$				53
L-glutamic acid		90	15	54-57
L-glutamine		90	15	54-57
L-alanine		55	21	57,64
L-asparagine				58
L-valine		6.8-26		55
L-leucine		6.8-26		55
1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea	4.6-21	0.3-1.5	60-65	59
bis(2-chloroethyl)-nitrosourea	20-40	15-20	60	60

are characterized by fast reaction times and specific stereochemistries. Examples of some of the enzyme reactions used are shown in Figure 2.

Figure 2. Enzymatic syntheses of ^{13}N -labelled amino acids (references 54-58)

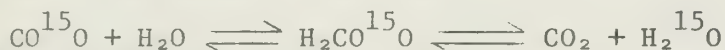


In the only chemical synthesis involving ^{13}N , Pettit et al.^{59,60} prepared HO^{13}NO by oxidation of $^{13}\text{NH}_3$ with oxygen and a $\text{Ga}_2\text{O}_5\text{-CoO}$ catalyst; the labelled nitrous acid was used to synthesize 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and bis(2-chloroethyl)nitrosourea (BCNU); the ^{13}N label was incorporated in the nitroso group of the final product.

^{15}O -Labelled Compounds. Oxygen-15 has the shortest half-life of the isotopes discussed here: 2.04 minutes. This isotope of oxygen is usually produced by the $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$ reaction.⁶¹

Very few applications of oxygen-15 have been reported. Formation of ^{15}O gas can be accomplished by deuteron bombardment of nitrogen gas and C^{15}O and CO^{15}O produced by passage of ^{15}O over activated charcoal at 900 and 400°C, respectively.⁶¹ These gases are presently used in clinical studies of pulmonary function.

Water as the oxygen-15 containing entity can be prepared by dissolving CO^{15}O in unlabelled water, with the following reaction occurring:



The only major application of oxygen-15 has been the preparation of labelled oxyhemoglobin and carboxyhemoglobin by dissolving ^{15}O and C^{15}O in blood. These labelled hemoglobins are then used in the measurement of cerebral blood flow, blood volume, and oxygen metabolism.^{62,63}

Conclusions. The use of carbon-11, nitrogen-13, and oxygen-15 in the synthesis of radiopharmaceuticals is of growing importance, and such labelled compounds hold promise in the detection and treatment of medical problems. These radionuclides may also find use in the study of the in vivo distribution and metabolism of toxic chemicals.

BIBLIOGRAPHY

1. R. E. Counsell and R. D. Ice, "The Design of Organ-Imaging Radiopharmaceuticals", in Drug Design, J. Ariens, Ed., Academic Press, N.Y., N.Y., 1975, pp. 172-257.
2. A. P. Wolf and C. S. Redvanly, Int. J. Appl. Radiat. Isot., **28**, 29 (1977).
3. M. G. Straatmann, Int. J. Appl. Radiat. Isot., **28**, 13 (1977).

4. G. Friedlander, J. W. Kennedy, and J. M. Miller, Nuclear and Radio-Chemistry, John Wiley, N.Y., N.Y., 1964.
5. A. Donnerhack, E. L. Sattler, and W. Trampsich, Strahlentherapie, 151, 240 (1976).
6. J. S. Fowler, A. N. Ansari, R. R. MacGregor, H. L. Atkins, and A. P. Wolf, J. Med. Chem., 17, 246 (1974).
7. D. R. Christman, R. M. Hoyte, and A. P. Wolf, J. Nuc. Med., 11, 474 (1970).
8. W. Vaalburg, S. Reiffers, E. Beerling, J. J. Pratt, M. G. Woldring, and H. Wynberg, J. Labelled Comp., 13, 200 (1977).
9. J. S. Fowler, A. N. Ansari, H. L. Atkins, P. R. Bradley-Moore, R. R. MacGregor, and A. P. Wolf, J. Nucl. Med., 14, 867 (1973).
10. H. J. Machulla, P. Laufer, and G. Stocklin, Radiochem. Radioanal. Lett., 18, 275 (1974).
11. B. Langstrom and H. Lundqvist, Int. J. Appl. Radiat. Isot., 27, 351 (1976).
12. M. G. Straatman, A. G. Hartmann, and M. J. Welch, J. Labelled Comp., 10, 175 (1974).
13. C. Marazano, M. Maziere, G. Berger, and D. Comar, Int. J. Appl. Radiat. Isot., 28, 49 (1977).
14. W. G. Myers, J. Nucl. Med., 13, 699 (1972).
15. M. E. Raichle, J. O. Eichlung, M. G. Straatmann, M. J. Welch, K. B. Larson, and M. M. Ter-Pogossian, Am. J. Physiol., 230, 543 (1976).
16. J. A. DeGrazia, A. F. Rodder, J. O. Teresi, P. D. Busick, and D. R. Walz, J. Nucl. Med., 16, 73 (1975).
17. A. J. Palmer and R. W. Goulding, J. Labelled Comp., 10, 627 (1971).
18. K. Weimer, Dissertation, Univ. Darmstadt, Germany (1973).
19. M. B. Winstead, J. F. Lamb, and H. S. Winchell, J. Nucl. Med., 14, 747 (1973).
20. D. Frost, L. Michel, and E. Schwarz, Strahlentherapie, 127, 510 (1965).
21. A. Donnerhack, E. L. Sattler, and W. Trampisch, Strahlentherapie, 151, 250 (1976).
22. W. Vaalburg, Thesis, Rijksuniversiteit, Groningen, Netherlands (1974).
23. W. Vaalburg, H. D. Beerling-V. der Molen, and M. G. Woldring, Nuclear-Medizin, 14, 60 (1973).
24. M. Vaalburg, H. D. Beerling-van der Molen, S. Reiffers, A. Rijskamp, M. G. Woldring, and H. Wynberg, Int. J. Appl. Radiat. Isot., 27, 153 (1976).
25. L. C. Washburn, T. T. Sun, B. W. Wieland, and R. L. Hayes, J. Nuc. Med., 16, 579 (1975).
26. S. J. DeNardo, E. J. Hershgold, G. L. DeNardo, K. A. Krohn, and D. R. Godin, J. Nucl. Med., 18, 472 (1977).
27. G. Gundlach, E. L. Sattler, W. Trampisch, and U. Wagenbach, Z. Naturforsch., 31, 377 (1975).
28. A. N. Ansari, H. Atkins, J. Briggs, D. Christman, J. S. Fowler, B. Gallagher, R. MacGregor, and A. P. Wolf, J. Nucl. Med., 16, 511 (1975).
29. J. S. Fowler, B. M. Gallagher, R. R. MacGregor, A. P. Wolf, A. N. Ansari, and H. L. Atkins, J. Med. Chem., 19, 356 (1976).
30. D. R. Christman, R. D. Finn, K. I. Karlstrom, and A. P. Wolf, J. Nucl. Med., 14, 864 (1973).
31. M. J. Welch, R. E. Coleman, M. G. Straatmann, B. E. Asberry, J. L. Primeau, W. S. Fair, and M. M. Ter-Pogossian, J. Nucl. Med., 18, 74 (1977).
32. M. Maziere, G. Berger, and D. Comar, J. Labelled Comp., 13, 196 (1977).

33. G. A. Andrews, K. F. Hubner, L. C. Washburn, B. W. Wieland, W. D. Gibbs, R. L. Hayes, T. A. Butler, and I. R. Collmann, *J. Nuc. Med.*, 18, 638 (1977).
34. S. Reiffers, E. Beerling, W. Vaalburg, W. ten Hoeve, W. C. Woldring, and H. Wynberg, *J. Labelled Comp.*, 13, 198 (1977).
35. M. B. Winstead, P. J. Widner, R. L. Means, M. A. Engstrom, G. E. Graham, A. Khentigan, T. H. Lin, J. F. Lamb, and H. S. Winchell, *J. Nucl. Med.*, 16, 1049 (1975).
36. J. F. Lifton and M. J. Welch, *Int. J. Radiat. Res.*, 45, 35 (1971).
37. M. G. Straatmann, and M. J. Welch, *Int. J. Appl. Radiat. Isot.*, 24, 234 (1973).
38. A. J. Palmer and R. W. Goulding, *J. Labelled Comp.*, 10, 627 (1974).
39. M. B. Winstead, S. J. Pan, I. H. Lin, A. Khentigan, J. Lamb, and H. S. Winchell, *J. Nucl. Med.*, 13, 479 (1972).
40. M. B. Winstead, S. J. Pan, M. J. Rogal, P. S. Brockman, and R. Lubner, *J. Med. Chem.*, 19, 279 (1976).
41. R. S. Tilbury, S. Stavchansky, C. T. Ting, J. M. MacDonald, E. Maugham, B. R. Freed, G. R. Russ, L. Helson, R. S. Benua, H. B. Kostenbader, and J. S. Laughlin, *J. Nucl. Med.*, 16, 575 (1976).
42. D. R. Christman, E. J. Crawford, M. Freidkin, and A. P. Wolf, *Proc. Nat. Acad. Sci. U.S.A.*, 69, 988 (1972).
43. M. G. Straatman and M. J. Welch, *J. Nucl. Med.*, 16, 425 (1975).
44. C. Marazano, M. Maziere, J. L. Margat, P. De La Llosa, D. Comar, and D. Fromageot, *Radiochem. Radioanal. Lett.*, 21, 53 (1975).
45. J. C. Clark, H. I. Glass, and D. J. Silvester, *Proc. 2nd Int. Conf. Methods Prep. Stor. Labelled Cmpds.*, J. Sirchis, ed., EURATOM, Brussels, Belgium, 1966.
46. H. I. Glass, A. Brandt, J. C. Clark, A. C. De Garrata, and L. G. Day, *J. Nucl. Med.*, 9, 571 (1968).
47. H. I. Glass, A. C. De Garrata, S. M. Lewis, P. Grammaticos, and L. Szur, *Lancet*, 1, 669 (1968).
48. L. Spolter, C. C. Chang, D. Bobinet, M. B. Cohen, N. S. MacDonald, A. Flesher, and J. Takahashi, *J. Nucl. Med.*, 16, 572 (1975).
49. D. Comar, M. Maziere, and C. Crouzel, *Radiopharmaceuticals and Labelled Compounds*, Vol. I, p. 461, IAEA, Vienna, 1973.
50. R. L. Hayes, I. C. Washburn, B. W. Wieland, T. T. Sun, R. R. Turtle, and T. A. Butler, *J. Nucl. Med.*, 17, 748 (1976).
51. R. L. Hayes, L. C. Washburn, B. W. Wieland, and T. T. Sun, *J. Nucl. Med.*, 18, 639 (1977).
52. S. C. Jones, W. M. Bucelewicz, R. A. Brissette, R. Subramanian, and B. Hoop, *Int. J. Appl. Radiat. Isot.*, 28, 25 (1977).
53. R. A. Lathrop, P. V. Harper, B. H. Rich, R. Dinwoodie, H. Krizek, N. Lembares, and I. Gloria, *Radiopharmaceuticals and Labelled Compounds*, Vol. I, p. 471, IAEA, Vienna, 1973.
54. M. G. Straatmann and M. J. Welch, *Radiat. Res.*, 56, 48 (1973).
55. M. B. Cohen, L. Spolter, N. MacDonald, D. T. Masuoka, S. Laws, H. H. Neely, and J. Takahashi, *Radiopharmaceuticals and Labelled Compounds*, Vol. I, p. 483, IAEA, Vienna, 1973.
56. A. S. Gelbard, L. P. Clarke, J. M. McDonald, W. G. Monahan, R. S. Tilbury, T. Y. T. Kuo, and J. S. Laughlin, *Radiology*, 116, 127 (1975).
57. M. B. Cohen, L. Spolter, N. MacDonald, C. C. Chang, and J. Takahashi, in *Radiopharmaceuticals*, G. Subramanian, B. A. Rhodes, J. F. Cooper, and V. J. Sodd, eds., Soc. Nuclear Medicine, N.Y., N.Y., 1975.
58. A. S. Gelbard, L. P. Clarke, and J. S. Laughlin, *J. Nuc. Med.*, 15, 1223 (1974).
59. W. A. Pettit, R. M. Mortara, G. A. Digenis, and M. F. Reed, *J. Med. Chem.*, 18, 1029 (1975).

60. W. A. Pettit, R. S. Tilbury, G. A. Digenis, and R. H. Mortara, J. .
Labelled Comp., 13, 119 (1977).
61. M. J. Welch and M. M. Ter-Pogossian, Radiat. Res., 36, 580 (1968).
62. C. C. Carter, J. O. Eichlung, D. O. Davis, and M. M. Ter-Posossian,
Neurology, 22, 755 (1972).
63. J. O. Eichlung, M. E. Raichle, R. L. Grubb, K. B. Larson, and M. M.
Ter-Pogossian, Circ. Res., 37, 707 (1975).
64. L. Spolter, M. B. Cohen, C. C. Chang, and N. S. MacDonald, J.
Labelled Comp., 13, 204 (1977).

BALDWIN'S RULES FOR RING CLOSURE

Reported by Daniel F. Heiman

February 9, 1978

A discussion of the Walden inversion mechanism for S_N2 reactions at saturated carbon centers, with its preferred angle of attack aligned 180° from the leaving group, has been a standard feature of elementary organic chemistry textbooks for many years (Figure 1).¹ Less well known is the recent definitive work of Burgi and Dunitz delineating the preferred angle of approach of a nucleophile to the sp^2 -hybridized carbon atom of a carbonyl group. Based on both X-ray crystallographic data² and quantum mechanical calculations,³ they have shown that the nucleophile tends to approach in a plane passing through the carbon-oxygen bond perpendicular to the plane defined by the oxygen atom and the two R-groups and at an angle of 102 to 114° with respect to the $C=O$ bond direction (Figure 2).⁴ This angle of attack is approximately the angle the nucleophile will assume with respect to the carbon-oxygen bond in the tetrahedral product of the addition. Much less information is available concerning the approach of reactants to an sp -hybridized center, but several X-ray crystallographic studies on acetylenes suggest that in a polymerization reaction, the attacking (radical) species may be oriented so as to approach at an angle of 120° with respect to the $C-R$ single bond, again assuming the angular relationship that these atoms will maintain in the product of the addition (Figure 3).⁵

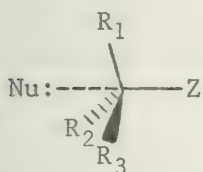


Figure 1

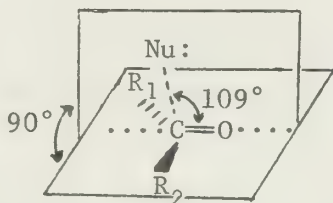


Figure 2

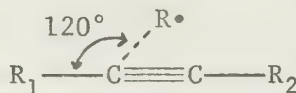


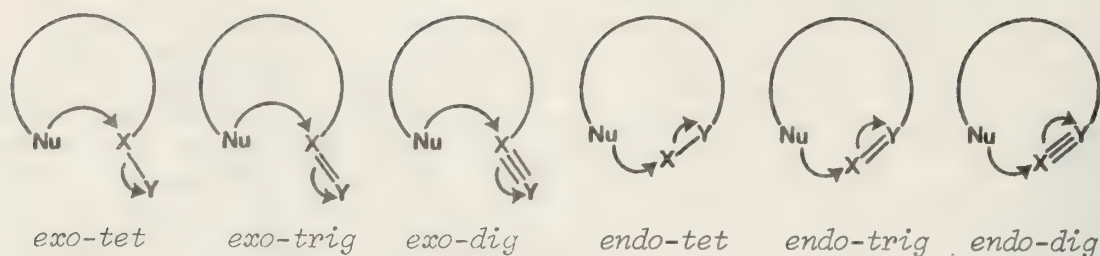
Figure 3

On the basis of this information and with the aid of the large body of literature which deals with the synthesis of cyclic compounds, Dr. J. E. Baldwin has drawn up a set of Rules for Ring Closure which classify ring-forming reactions as favorable or unfavorable as a function of the ring size and the reaction type involved.⁶ A cyclization is called *exo-* if the leaving group (or pair of electrons) is expelled from the smallest ring formed. It is called *endo-* if the pair of electrons (or leaving group) is displaced into the ring. The suffix *-tet* denotes a displacement occurring at a tetrahedral center; *-trig* and *-dig* are applied to reactions at trigonal (sp^2 -hybridized) and digonal (sp -hybridized) centers, respectively (Scheme I).⁷ A numerical prefix describes the size of the ring being formed.

The Rules are as follows:

- 1) Tetrahedral Systems: 3- to 7-*exo-tet* are all favored; 5- and 6-*endo-tet* are disfavored.
- 2) Trigonal Systems: 3- to 7-*exo-trig* are all favored; 3- to 5-*endo-trig* are disfavored; 6- and 7-*endo-trig* are favored.
- 3) Digonal Systems: 3- and 4-*exo-dig* are disfavored; 5- to 7-*exo-dig* are favored, and 3- to 7-*endo-dig* are all favored.

Scheme I



The Rules apply only for cases where relatively moderate activation energies are available (i.e., not for photolyses or extremely high temperature reactions) and only for cases in which both of the reacting termini are first row elements, since the preferred angles of attack vary from those described above when d-orbitals are involved in the bonding.⁸ It is also clear that conjugation or the presence of substituents capable of resonance donation (such as nitrogen) may produce apparent exceptions to the Rules by modifying the preferred angle of approach to a carbonyl group.⁹ It is important to analyze each reaction with respect to the nucleophilic as well as the electrophilic moiety: An enolate ion cyclizing in an exocyclic manner, but with electron flow away from the sp^2 -hybridized center rather than toward it, follows the Rules for *exo-trig* systems, and a similar reverse endocyclic closure behaves as an *endo-trig* system.¹⁰

In addition to surveying the literature for reactions which provide empirical support for his Rules,¹¹ Dr. Baldwin has reported a number of experiments of his own which confirm their validity.¹² The Rules are finding acceptance in the chemical community. Other workers have used them in planning syntheses,¹³ in explaining negative results,¹⁴ and in elucidating the mechanisms of reactions.¹⁵

BIBLIOGRAPHY

1. (a) P. Walden, *Chem. Ber.*, **32**, 1855 (1899); (b) W. A. Cowdry, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937); (c) L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).
2. (a) H. B. Bürgi, *Angew. Chem. Int. Ed. Engl.*, **14**, 460 (1975); (b) H. B. Bürgi, J. D. Dunitz, J. M. Lehn, and G. Wipff, *Tetrahedron*, **30**, 1563 (1974); (c) H. B. Bürgi, J. D. Dunitz, and E. Scheffer, *J. Am. Chem. Soc.*, **95**, 5065 (1973).
3. H. B. Bürgi, J. M. Lehn, and G. Wipff, *J. Am. Chem. Soc.*, **96**, 1956 (1974) and references 2a) and 2b).
4. See also D. C. Wigfield and F. W. Gowland, *J. Org. Chem.*, **42**, 1108 (1977).
5. (a) R. H. Baughman, *J. Appl. Phys.*, **43**, 4362 (1972); (b) G. Wegner, *Polymer Lett.*, **9**, 133 (1971).
6. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
7. Note that in the *endo-tet* case, the result is a group transfer rather than ring formation.

8. J. E. Baldwin, J. Cutting, W. DuPont, L. Kruse, L. Silberman, and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 736 (1976).
9. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 738 (1976); see also R. Suess, *Helv. Chim. Acta*, 60, 1650 (1977) and C. Agami, *Tetrahedron Lett.*, 2801 (1977).
10. J. E. Baldwin and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 233 (1977).
11. Approximately 20 synthetic papers are cited in references 6 and 10.
12. J. E. Baldwin and J. A. Reiss, *J. Chem. Soc., Chem. Commun.*, 77 (1977) and reference 8.
13. R. J. Stoodley, *Chem. Ind. (Lond.)*, 377 (1977).
14. (a) S. P. Mariano, M. E. Osborn, D. Mariano, B. C. Gunn, and R. C. Pettersen, *J. Org. Chem.*, 42, 2903 (1977); (b) J. W. Hines and C. H. Stammer, *J. Med. Chem.*, 20, 965 (1977).
15. (a) B. G. Chatterjee and D. P. Sahu, *J. Org. Chem.*, 42, 3162 (1977); (b) E. G. Scovell and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 275 (1977); (c) R. J. DePasquale, *J. Org. Chem.*, 42, 2185 (1977); (d) M. E. Kuehne and R. E. Damon, *ibid.*, 42, 1825 (1977); (e) R. E. Merrill, J. L. Allen, A. Abramovitch, and E. Negishi, *Tetrahedron Lett.*, 1019 (1977).

STEREOSELECTIVE ALLYLIC COUPLINGS

Reported by P. M. Savu

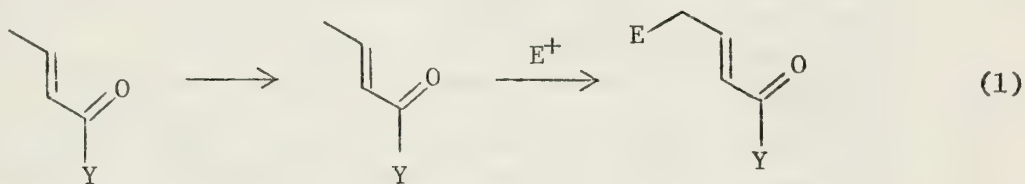
February 13, 1978

One approach to olefin synthesis involves the coupling of an allyl unit with some electrophile or nucleophile. One of the possible ionic modes of coupling is the reaction of an allyl anion with an electrophile, although subject to complications due to the fact that the charge becomes delocalized in the allyl unit. Complex mixtures of products may result from the reactions. Several strategies have been tried in order to overcome the problem.

One strategy used by Katzenellenbogen and Lenox¹ was to decrease the lifetime of the reactive intermediate by the generation of allyl lithium compounds in the presence of electrophiles. Another strategy was to use a transition metal to influence the course of the reaction. Addition of CuI to solutions of various allyl Grignard reagents led to exclusive alkylation at the carbon where the halide was attached previously.²

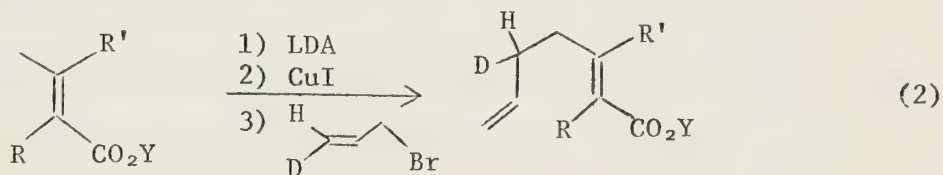
A stabilizing group can be used to generate a charge at an allylic carbon and effect alkylation selectively at one end or the other of the allyl anion. The stabilizing group can be located alpha to the desired alkylation site and direct reaction at that center. Groups such as sulfone,^{3,4} sulfoxide,⁵ sulfide,^{6,7} carbonyl,⁸ or alkylphosphonium bromide⁹ have been used.

In some cases the stabilizing group can be located gamma to the desired alkylation site. Allyl ethers^{10,11} have been alkylated in this fashion. Theoretically, an α,β -unsaturated carbonyl compound is also capable of this type of stabilization.



α,β -Unsaturated ketones,¹² aldehydes,¹³ and aldimines¹⁴ have been found to react predominantly at the alpha carbon. Alkylation has been directed to the gamma carbon to varying degrees in the cases of α,β -unsaturated esters,¹⁵⁻¹⁸ acids,¹⁹⁻²³ and amides.^{24,25}

Addition of CuI to the anion of α,β -unsaturated carbonyl compounds to form a "carbon dienolate" has been found to increase dramatically the relative amount of gamma alkylation in the case of α,β -unsaturated esters,^{26,27} acids,^{28,29} and amides.³¹ With acids and esters, attack on an allylic electrophile has been found to be effectively $\text{S}_{\text{N}}2'$ when that carbon is unhindered (Eq. 2).^{26,28}



In the case of "copper dienolates" of α,β -unsaturated acids, the high percentage of gamma alkylation has been obtained only with allylic electrophiles.³⁰ High percentages of γ products have been obtained when the "copper dienolates" of α,β -unsaturated amides were alkylated with allylic and non-allylic electrophiles.³¹

BIBLIOGRAPHY

1. J. A. Katzenellenbogen and R. S. Lenox, *J. Org. Chem.*, **38**, 326 (1973).
2. F. Derguini-Boumechal, R. Lorne, and G. Linstrumelle, *Tetrahedron Lett.*, 1181 (1977).
3. P. A. Grieco and Y. Masaki, *J. Org. Chem.*, **39**, 2134 (1974).
4. D. Savoia, C. Trombin, and A. Umani-Ronchi, *J. Chem. Soc., Perkin I*, 123 (1977).
5. P. J. R. Nederlof, M. J. Moolenaar, E. R. de Waard, and H. O. Huisman, *Tetrahedron Lett.*, 579 (1977).
6. J. F. Bielman and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969).
7. P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin I*, 1131 (1977).
8. R. M. Carlson and A. R. Oyler, *J. Org. Chem.*, **41**, 4065 (1976).
9. E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Am. Chem. Soc.*, **92**, 2139 (1970).
10. D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974).
11. W. C. Still and T. L. Macdonald, *J. Am. Chem. Soc.*, **96**, 5561 (1974).
12. H. E. Zimmerman, "Molecular Rearrangements", ed. Pide Mayo, Interscience, N.Y., 1963, p. 345.
13. S. A. G. de Graaf, P. E. R. Dosterhoff, and A. van der Gen, *Tetrahedron Lett.*, 1653 (1974).
14. K. Takabe, H. Fujuuara, T. Katagiri, and J. Tanaka, *Tetrahedron Lett.*, 1237 (1975).
15. P. E. Blatz, P. Balasubramaniyan, and V. Balasubramaniyan, *J. Am. Chem. Soc.*, **90**, 3282 (1968).
16. G. A. Koppel, *Tetrahedron Lett.*, 1507 (1972).
17. A. Kajikawa, M. Mousaki, and N. Ikekawa, *Tetrahedron Lett.*, 4135 (1975).
18. E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **39**, 821 (1974).
19. K. Suga, S. Watanabe, and T. Fujita, *Australian J. Chem.*, **25**, 2393 (1972).
20. S. Watanabe, K. Suga, T. Fujita, and F. Fujujoshi, *Chem. Ind.*, 80 (Jan., 1972).
21. P. E. Pfeffer, L. S. Silber, and E. Kinsel, *Tetrahedron Lett.*, 1163 (1973).
22. B. S. Pitzele, J. S. Baran, and D. H. Steinman, *J. Org. Chem.*, **40**, 269 (1975).
23. C. A. Hendrick, W. E. Willy, D. R. McKeàn, E. Baggiolini, and J. B. Siddall, *J. Org. Chem.*, **40**, 8 (1975).
24. J. F. Wolfe, G. B. Trimitsis, and D. R. Morris, *J. Org. Chem.*, **34**, 3263 (1969).
25. A. Wu and V. Snieckus, *Tetrahedron Lett.*, 2057 (1975).
26. J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5664 (1974).
27. J. A. Katzenellenbogen, Ph.D. Thesis, Harvard, Cambridge, Mass., 1969, p. 175.
28. J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **98**, 4925 (1976).
29. B. S. Pitzele, J. S. Baran, and D. H. Steinman, *Tetrahedron*, **32**, 1347 (1976).

30. J. A. Katzenellenbogen and P. M. Savu, unpublished work.
31. J. A. Oakleaf, M. T. Thomas, A. Wu, and V. Snieckus, Tetrahedron Lett., in press.

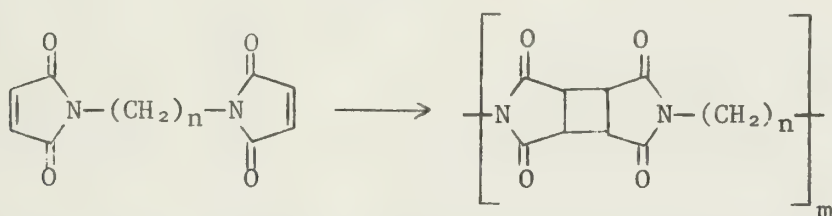
RADIATION-INITIATED CATIONIC POLYMERIZATIONS

Reported by Brian Dixon

February 16, 1978

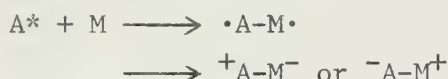
The use of high energy radiation as a means of initiating polymerization is a subject studied since the mid-nineteenth century. The recent energy crisis has caused a resurgence of interest industrially, since photoinitiation offers significant potential energy and cost savings. A wide range of photoinitiators has been studied, covering both organic and inorganic types.¹ In addition, there are three main categories of photoinduced polymerizations. First is the barely explored field of photocondensation polymerization.^{2,3} Here, advantage is taken of the cycloaddition phenomenon to introduce unusual structural features. In an exemplary case, cyclobutane rings, certainly rare in polymer chemistry, can be made via [2+2] cycloaddition (Scheme I).

Scheme I



Second is the well established and much studied field of photoinitiated free radical vinyl polymerization.^{1,4-7} Here, vinyl monomers are polymerized by typical free radical mechanisms and kinetics. Most commonly, initiation is accomplished via intermediate photoexcited carbonyl compounds. In principle, there are at least five distinct mechanisms by which a photoexcited molecule (A^* or AB^*) may initiate polymerization:

- A. Direct addition of A^* to monomer (M) producing a biradical or dipolar species, e.g.:



- B. Energy transfer from primarily triplet excited molecules to produce triplet excited monomers, e.g.:



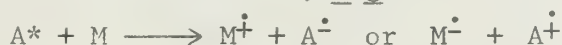
- C. Homolytic fragmentation of a photoexcited molecule, e.g.:



- D. Hydrogen abstraction by A^* from monomer, solvent, impurities, etc., to produce two radicals, e.g.:

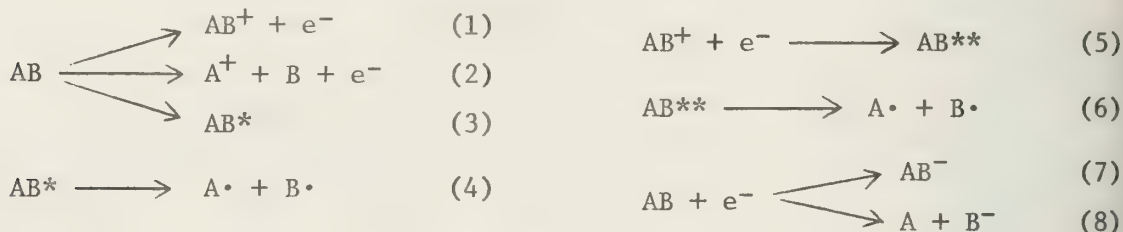


- E. Electron transfer between photoexcited molecules and monomer to produce ion radicals, e.g.:



The aromatic carbonyl compounds related to and including benzo-phenone are by far the most widely studied and used photoinitiators.

The third basic category of photoinduced polymerizations is comprised of cationic and anionic initiators. While neither of these types has been examined extensively, anionic photopolymerization appears to be a rare phenomenon. The only example known is the polymerization of nitroethylene using THF as solvent. The anionic nature of the polymerization is indicated by copolymerization studies with acrylonitrile. Cationic photopolymerization, which has been studied more intensively, is the subject with which the remainder of this seminar deals. Cationic initiating species can be generated, as can anionic and free radical types, by interaction with high energy or "ionizing" radiation. The energy sources used produce UV or gamma radiation. The following studies all involved gamma radiation. A molecule, AB, upon being irradiated with gamma rays, may undergo the following transformations:



The relative probabilities of the cation-producing reactions (1) (direct ionization) and (2) (dissociative ionization) are not known for condensed systems. The anion-producing reactions (7) and (8) occur in significant yield only in media where species of high electron affinity are present. The fate of the electron produced in the cation-forming reactions in a non-polar medium, such as pure hydrocarbon, is still in dispute. This is a problem directly related to the understanding of ionic polymerization in systems such as neat styrene or isobutylene.

The study of cationic initiation necessarily involves the simultaneous study of free radical initiation since the latter invariably occurs with the former under high energy radiation conditions. Which mechanism prevails is dependent upon the monomer being studied and upon the experimental conditions. The major factors affecting the mechanism include reaction medium, temperature, and dose rate. Several techniques are used to determine the relative amounts of cationic and free radical mechanisms. Of these, the use of selective inhibitors and the study of the composition of copolymer formed under analogous conditions have given the best results.

Inhibitors. Benzoquinone has been used extensively as a free radical inhibitor of polymerization. But being an efficient electron scavenger (like most of the free radical inhibitors), it is not inert to the cationic process. On the other hand, ionic species inhibitors, such as water, pyridine, and ammonia, have little effect on the free radical process. Nevertheless, some very interesting results have been obtained with benzoquinone. Figure 1 shows an Arrhenius plot of the rate of polymerization of styrene in the absence and presence of benzoquinone.⁹ This graph is striking in that the linear plot (b), where inhibitor is present, is believed to be the ionic contribution to the rate. As expected for ionic polymerizations, the rate increases as the temperature decreases. Curve (a) is the rate without inhibitor present and represents the overall

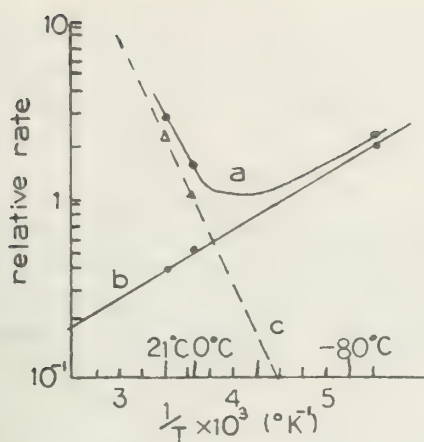


Figure 1. Rate of styrene polymerization in dichloroethane. a-no additives; b-with benzoquinone; c-result of $a - b$.

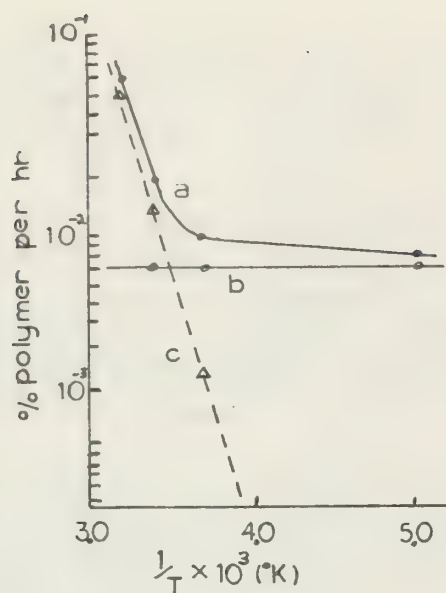


Figure 2. Rate of bulk styrene polymerization. Same code as Figure 1, except DPPH used as inhibitor.

rate of the combined mechanisms. Plot (c) is obtained by subtracting the ionic contribution (b) from (a) and is the free radical contribution to the rate.

Figure 2 shows a similar plot for isoprene with diphenylpicrylhydrazyl as the selective inhibitor.¹⁰ Here, DPPH was found to inhibit strongly the polymerization at temperatures near 20°C, while inhibition by pyridine was found to be stronger at lower temperatures. These results indicate that the polymerization proceeds by an ionic mechanism at lower temperatures and by a radical mechanism at higher temperatures. The fact that the curved diagram obtained in the absence of inhibitor can be resolved into two linear plots suggests that the free radical and cationic mechanisms occur side by side with very little interaction between them. The activation energies observed for these cationic reactions are very small or negative, being -2.5 kcal/mole for styrene in dichloroethane.⁹

Dose Rate. In the preceding experiment, no special care was taken to remove traces of water from the system. Under these conditions, the cationic contribution to the reaction at room temperature is only a small fraction of the free radical contribution. It is well known that the rate of free radical polymerization varies as the square root of the radiation dose rate, while the cationic rate varies directly with the dose rate. Thus, the relative contribution of the cationic process should increase as the dose rate does. Figure 3 shows the influence of dose rate on the bulk polymerization of "wet" styrene with and without added benzoquinone. When inhibitor is present, the polymerization is not completely inhibited at room temperature but proceeds slowly at a constant rate until the benzoquinone is used up.¹¹ The slopes of the two curves in Figure 3 suggest that in this case, that of "wet styrene", the cationic and free radical rates should be equal at dose rates of around 10^3 rd/sec. Recent experiments of Squire *et al.*¹² with "wet styrene" at high dose rates support this prediction. Squire's results are plotted in

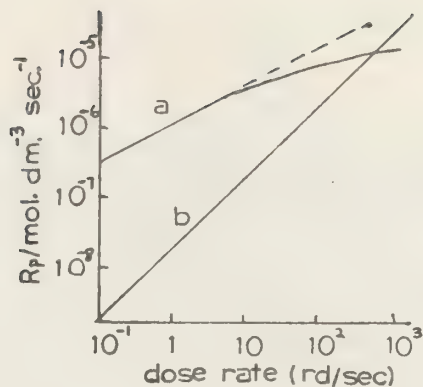


Figure 3. Log-log plot of "wet" styrene polymerization rate versus dose rate. a-no additives; b-1% benzoquinone.

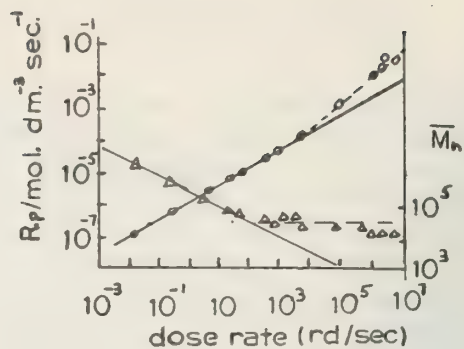


Figure 4. Same code as Figure 3. (at 20°C) $\Delta \equiv$ change in \overline{M}_n with dose rate; $\circ \equiv$ change in polymerization rate.

Figure 4 on a log-log diagram. As can be seen, a deviation from the free radical mechanism square root dependence appears at dose rates above 10^3 rd/sec with the dose rate exponent increasing in rough proportion to the first power of the dose rate.¹² Figure 4 also shows the change of molecular weight with increasing dose rate. In a wholly free radical mechanism the molecular weight is expected to decrease linearly as a function of the square root of the dose rate. Figure 4 shows a leveling off at a molecular weight of 50,000. These results, obtained at very high dose rates, suggest that even at room temperature the radiation induced polymerization of styrene occurs at least partly by a cationic mechanism. Drying of the monomer progressively increases the importance of the cationic mechanism.

Copolymerizations. Monomer pair systems have been studied in which one (or both) of the monomers is able to undergo both free radical and cationic polymerization. Systems in point are: styrene-methyl methacrylate in chlorinated solvents,^{9,13} the bulk copolymerization of isobutylene-vinylidene chloride,¹³ and isoprene-MMA.¹⁴ Of these monomers, styrene, isobutylene, and isoprene, respectively, could be expected to undergo cationic polymerizations. In all three cases, the proportion of these "cationic" monomers in the copolymers was found to increase as the temperature was lowered, indicating a more pronounced cationic mechanistic contribution to the overall process.

A comparable situation exists with copolymers obtained from "wet" and "dry" ($<10^{-3}$ M water) monomer systems. Williams *et al.*¹⁵ found the rate of polymerization of isobutyl vinyl ether increased remarkably in a "dry" system, and they proposed a cationic polymerization mechanism. Ueno *et al.*¹⁶ found that copolymers of styrene and α -methyl styrene or isobutyl vinyl ether contained higher contents of styrene when the monomer mixture was dried over CaH_2 than when it was dried more rigorously over a Na-K alloy. However, neither in this study nor in another comparable one¹⁷ was an attempt made to fractionate the copolymer formed. Therefore, it is not known whether random copolymers of different composition or a mixture of homopolymer and copolymer or a block copolymer is formed. If both free radical and cationic mechanisms are occurring side

by side, a mixture of free radical copolymer and cationic homopolymers would be expected to grow. In addition, a block copolymer could be expected to form from a polymeric species, with one end being a carbonium ion and the other a radicaloid. Careful product analysis should clarify this point.

Pure Hydrocarbon Monomers. The study of pure hydrocarbon monomer polymerization looms as very important in the eventual understanding of the mechanism of chain propagation via free cations and the storage of electric charges in hydrocarbon media. Styrene, α -methylstyrene, and isobutylene are the most studied monomers; however, regardless of monomer, the overriding factor in published experiments is the technique used for drying the monomer.

Figures 5 and 6 show the effect of dehydration on the polymerization of styrene¹⁸⁻²⁰ and α -methylstyrene.²⁰⁻²¹ The curves differ in degree of dehydration, with the lower curve showing the behavior of "wet" monomer. Ueno²² also obtained similar results in the case of styrene. The lowest curve is essentially the case for the all free radical reaction of styrene, and the predicted square root law is obeyed. With α -methylstyrene, the dose rate exponent is closer to unity, indicating an ionic contribution. As the styrene drying becomes more rigorous, the overall rate of reaction goes up and the dose rate function approaches unity. This strongly suggests that cationic polymerization is occurring. Further drying eliminates more and more of the water termination, and the growing chains are terminated by negatively charged species formed directly by irradiation; thus, the square root function is again approached.

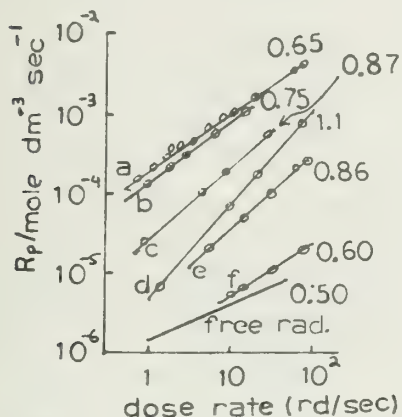


Figure 5. Log-log plot of styrene polymerization rate as a function of dose rate. Curve sequence f--a corresponds to progressively more dry monomer. Curve figures are the dose rate exponents.

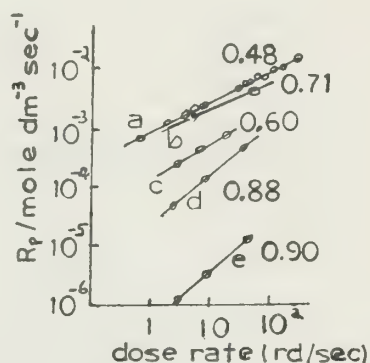


Figure 6. Same code as Figure 5, except for α -methylstyrene.

Figures 5 and 6 indicate that the rate of cationic polymerization may be 100 to 1000 times greater than the simultaneously occurring free radical reaction at the same dose rate. It is also noteworthy that the amount of water needed to be noticeable in an inhibitory sense is exceedingly small.

Ueno et al.^{16,22} have shown that in the case of styrene, significant retardation is observable by adding as little as 10^{-4} mole/l of water to styrene. It has also been demonstrated that careful, exhaustive drying of styrene, while drastically affecting its behavior in a radiation field, does not alter its polymerization when initiated by ultraviolet radiation or heat. Both of these initiations are believed to occur via free radical mechanisms.

It is interesting that super dry monomers such as styrene polymerize with very fast reaction rates, far higher than those observed in free radical polymerization. Since the radiation chemical yield of initiating ionic species is 10 to 50 times smaller than in the free radical case, the ratio of propagation to termination constants must be significantly higher in the cationic process. Estimated k_p 's for various monomers are given in Table 1. These k_p estimates are based on a combination of scavenger studies and electrical conductance measurements with stationary state conditions being assumed.^{19,22} It is noteworthy that the k_p of the "free" carbonium ion is far higher than that of conventional cationic polymerizations (ion pair in Table 1) where association with counter-ions is believed to occur. This suggests that with the super dry monomer, propagation is occurring via free ions in the radiation initiated reaction with no counter-ion being present in the immediate vicinity of the active chain end.

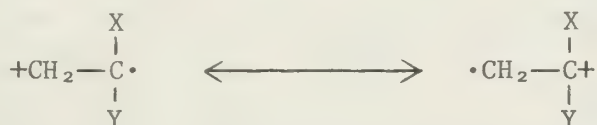
Table 1. Rate Constants for Propagation
in Super Dry Monomer Polymerization

Monomer	Propagating Species	Temp (°C)	k_p ($\text{dm}^3\text{mol}^{-1}\text{sec}^{-1}$)
styrene	carbonium ion	15	3.5×10^6
	ion pair	25	17
α -methylstyrene	carbonium ion	0	4×10^6
	" "	30	3×10^6
cyclopentadiene	" "	-78	6×10^8
isobutene	" "	0	1.5×10^8
isobutyl vinyl ether	" "	30	3×10^5

Reaction Mechanism.^{23,24} As compared to chemical initiation, radiation induced cationic initiation differs in one important aspect. Ionizing radiation produces initiating species at a low, constant rate, whereas chemical initiation produces the growing chains almost simultaneously. The importance of this observation lies in the fact that the concentration of growing chains formed by radiation initiation is usually very small. This means that stationary state conditions apply and the kinetics can be treated by the Bodenstein approximation.²⁵ Chemical initiation, however, is far more complex kinetically. Here, the propagation step may well be diffusion controlled. Since the diffusion rate steadily decreases with chain growth and concomitant viscosity increase,

the situation is seriously complicated. On the other hand, the initial events which give rise to cationic chains are not well understood. Lack of information concerning the precursors of cationic chains and fate of the charge carriers in organic media make the following section speculative.

Equations (1) and (2) given earlier represent the primary events thought to lead to positive ions in the reaction medium. It is reasonable to assume that for a monomer molecule the parent ion in Eq. (1) arises by ejection of a least tightly bound π electron, yielding a radical-cation species represented as:



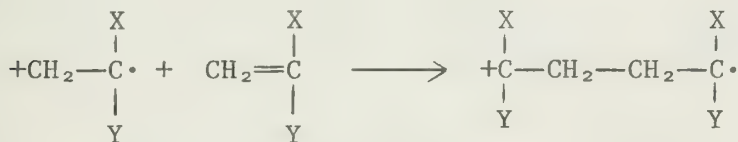
This species then may undergo a number of possible reactions, the most likely being:

(a) proton transfer from monomer:



This reaction readily occurs at low pressure in the mass spectrometer and thus could occur in condensed medium.

(b) addition to monomer:



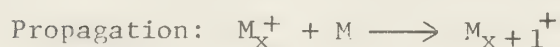
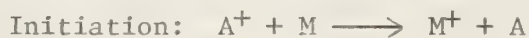
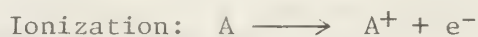
In both cases, free radical and cationic initiating species are generated side by side; thus, both mechanisms of polymerization are to be expected. This expectation is supported by the experimental evidence presented above. However, reaction (2) can subsequently occur as well, which may seriously complicate the situation early in the reaction. Although no good method of detecting the ionic intermediate in liquids presently exists, the most promising thus far is by pulse-radiolysis. Short-lived intermediates were detected in irradiated styrene and α -methylstyrene by their absorption, and the kinetics of decay have been investigated.^{20-21, 26-28} Unfortunately, detection of these intermediates is limited to the most absorbing species at concentrations high enough to produce measurable absorption.

Propagation. The propagation step in radiation-induced cationic initiation is the normal process unaffected by the mode of initiation (Scheme II). The situation is further simplified if chemical initiation and polar solvents are absent.

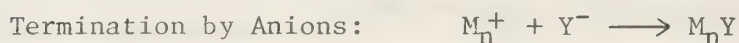
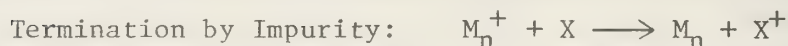
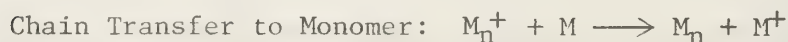
Chain Termination. Termination can occur by one of three means as in the conventional thermal process: (1) chain transfer to monomer, (2) termination by impurity, (3) termination by anion.

Scheme II represents the overall cationic process:

Scheme II



Termination:



Halogenated solvents also accelerate the rate of cationic polymerizations. This has been studied in conjunction with the photoinitiated grafting of isobutylene onto polyvinylchloride.²⁹⁻³⁰

BIBLIOGRAPHY

1. G. Oster and N. Yang, Chem. Rev., 68, 125 (1968).
2. F. C. DeSchryver, Pure Applied Chem., 34 (2), 213 (1973).
3. J. G. Higgins and D. A. McCombs, Chemtech, 176, March, 1972.
4. J. Hutchison and A. Ledwith, Adv. Poly. Sci., 14, 49 (1974).
5. H. G. Heine and H. J. Rosenkranz, Angew. Chem. Int. Ed., 11, 974 (1972).
6. A. Ledwith, J. Oil Col. Chem. Assoc., 59, 157 (1976).
7. S. S. Labana, J. Macromol. Sci.-Rev. Macromol. Chem., C 11 (2), 299 (1974).
8. M. Irie, S. Tomimoto, and K. Hayashi, J. Poly. Sci., Part B, 10, 699 (1972).
9. A. Chapiro and V. Stannett, J. Chim. Phys., 56, 830 (1959).
10. Y. Tabata, R. Shimozaawa, and H. Sobue, J. Polymer Science, 54, 201 (1961).
11. A. Chapiro, Plaste Kautschuk, 11, 451 (1964).
12. D. R. Squire, J. A. Cleaveland, T. M. A. Hossain, W. Oraby, E. P. Stahe, and V. Stannett, J. App. Polymer Sci., 16, 645 (1972).
13. A. P. Sheinker, M. K. Yokovleva, E. V. Kristalnyi, and A. D. Abkin, Dokl. Akad. Nauk. SSSR, 124, 632 (1959).
14. A. Hinschberger, M. Vacherot, and J. Marchal, C. R. Acad. Sci. (Paris), 263, 620 (1966).
15. M. A. Bonin, M. L. Calvert, W. L. Miller, and F. Williams, J. Poly. Sci., Part B, 2, 143 (1964).
16. K. Ueno, K. Hayashi, and S. Okamura, Polymer, 7, 431, 451 (1966).
17. A. I. Popova, A. P. Scheinker, and A. D. Abkin, Dokl. Akad. Nauk. SSSR, 157, 1192 (1964).

18. R. C. Potter, C. L. Johnson, D. J. Metz, and R. H. Bretton, *J. Poly. Sci., Part A-1*, 4, 419, 430 (1966).
19. R. C. Potter, R. H. Bretton, and D. J. Metz, *J. Poly. Sci., Part A-1*, 4, 2295 (1966).
20. D. J. Metz, *Advan. Chem. Ser. (Am. Chem. Soc., Washington)*, 91, 202 (1969).
21. D. J. Metz, *Advan. Chem. Ser. (Am. Chem. Soc., Washington)*, 66, 170 (1969).
22. K. Ueno, F. Williams, K. Hayashi, and S. Okamura, *Trans. Faraday Soc.*, 63, 1478 (1967).
23. F. Williams, *J. Macromol. Sci., Part A*, 6, 919 (1972).
24. A. Chapiro, *Makromol. Chem.*, 175, 1181 (1974).
25. F. Williams, K. Hayashi, K. Ueno, K. A. Hayashi, and S. Okamura, *Trans. Faraday Soc.*, 63, 1501 (1967).
26. M. Katayama, M. Hatada, K. Hirota, H. Yamazaki, and Y. Ozawa, *Bull. Chem. Soc. Japan*, 38, 851 (1965).
27. C. Schneider and A. J. Swallow, *J. Polymer Sci., Part B*, 4, 277 (1966).
28. C. Schneider, *Advan. Chem. Ser. (Am. Chem. Soc., Washington)*, 91, 219 (1969).
29. A. Chapiro and A. M. Jendrychowska-Bonamour, *C. R. Acad. Sci. (Paris)*, 265, 484 (1967).
30. M. Jendrychowska-Bonamour, *European Polymer J.*, 4, 627 (1968).

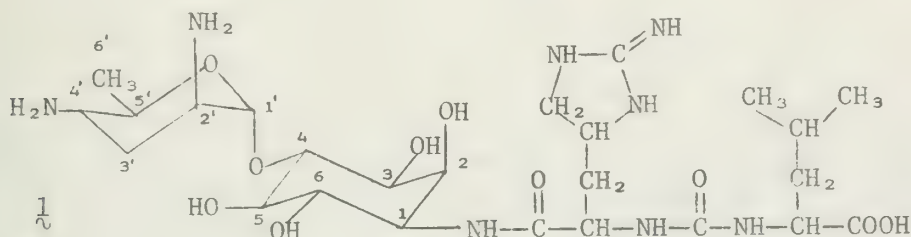
MINOSAMINOMYCIN: A GUANIDINE-CONTAINING ANTIBIOTIC

Reported by Michael T. Cheng

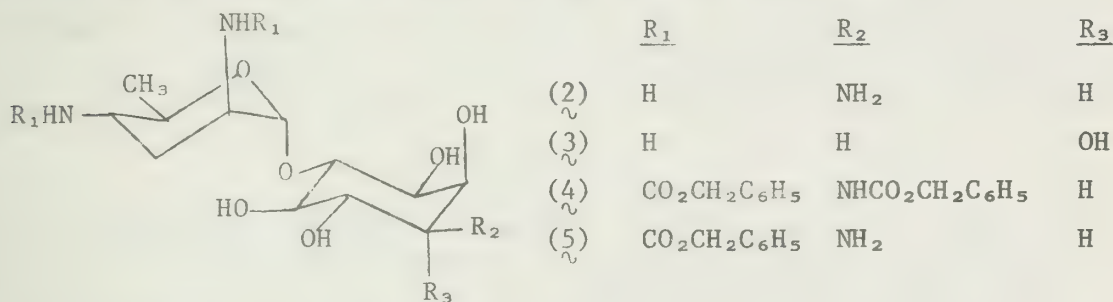
February 20, 1978

There are many guanidine-containing antibiotics, such as the streptomycins,¹ which have two mono-substituted guanidine groups, and minosaminomycin,² which has a di-substituted guanidine. Guanidine imparts two characteristic properties to molecules containing it: high polarity and basicity. To circumvent the difficulty one could: (1) hydrolyze the guanidine group by boiling in saturated aqueous barium hydroxide, as is in the case of the streptomycins,^{1a} (2) trimethylsilylate the guanidine nitrogens, as is the case with the antibiotic enduracidine,³ or (3) bring about condensation with 2,4-pentanedione to form a pyrimidine derivative if two of the guanidine nitrogens are unsubstituted.⁴

Minosaminomycine (1) is an antibiotic isolated from a culture filtrate of *Streptomyces* No. MA 514-A1 that inhibits the growth of mycobacteria. Chemically, Minosaminomycin, C₂₅H₄₆N₈O₁₀, consists of a sugar moiety myo-inosamine, and amino acids enduracididine and leucine.^{2b}



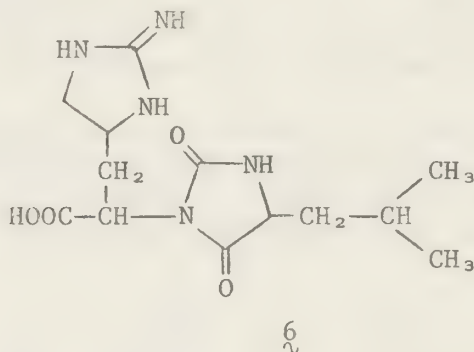
A new animocyclitol, 1D-1-amino-1-deoxy-myoinositol, was isolated by acid hydrolysis (6 N hydrochloric acid at reflux for 5 h) of minosaminomycin, together with a hydantoin derivative, a sugar derivative, a trace of leucine, and a basic glycoside named minobiosamine (2). The ¹H NMR of 2, upon comparison with that of kasuganobiosamine (3) obtained from kasugamycin,⁵ suggested the presence of the kasugamine moiety.



Benzyloxycarbonylation⁶ of 2 by the usual Schotten-Baumann procedure gave tri-N-benzyloxycarbonyl minobiosamine (4), which was treated with sodium hydride and then hydrolyzed with 5% barium hydroxide to afford di-N-benzyloxycarbonyl minobiosamine (5). Periodate oxidation of 5 followed by treatment with methanol and hydrochloric acid gave methyl di-N-benzyloxycarbonyl kasugaminide, which was identical with the kasugaminide derived from kasuganobiosamine⁵ in all respects.

Treatment of minobiosamine (2) with 2,2-dimethoxypropane, after acetylation, gave tri-N-acetyl-di-O-isopropylideneminobiosamine, mild acid hydrolysis of which gave tri-N-acetyl-2,3-O-isopropylidenemino-biosamine. This indicates that kasugamine must be glycosidically linked to the 4-OH or the 6-OH of the aminoinositol moiety. ¹H NMR analysis indicated that the structure of the minobiosamine is 1D-1-amino-1-deoxy-4-O-kasuganimyl-myo-inositol.

Complete acid hydrolysis of the hydantoin derivative (6) gave leucine and a basic amino acid. Titration of the mono-acetic acid salt of this



amino acid gave pK_a values of 2.5, 4.7, (acetic acid), 8.3, and 12. In addition to the strong basic function, high nitrogen content suggested the presence of a guanidine group. Permanganate oxidation of the basic amino acid afforded guanidine, which was characterized as the picrate.⁷ However, the negative Sakaguchi test⁸ indicated that the guanidine group is not mono-substituted. With the above information, plus NMR and mass spectrometry data, this amino acid was identified as enduracididine, which is one of the amino acids of the peptide antibiotic enduracidine.³

Furthermore, the structure of minosaminomycin has been confirmed by a partial synthesis. L-Leucine benzyl ester hydrochloride was treated with trichloromethyl chloroformate and then treated with the amino acid enduracididine. The product was then coupled with 5 by the active ester method,⁹ followed by catalytic hydrogenation, to afford synthetic minisaminomycin in 7% yield from L-leucine benzyl ester hydrochloride. The synthetic minosaminomycin was confirmed to be identical with the natural one in all respects including biological activity.

BIBLIOGRAPHY

1. (a) R. U. Lemieux and M. L. Wolform, *Advances in Carbohydrate Chemistry*, **3**, 337 (1948); (b) S. Neidle, D. Rogers, and M. B. Hursthouse, *Tetrahedron Lett.*, 4725 (1968).
2. (a) M. Hamada, S. Kondo, T. Yokoyama, K. Miura, K. Iinuma, H. Yamamoto, K. Maeda, T. Takeuchi, and H. Umezawa, *J. Antibiotics*, **27**, 81 (1974); (b) K. Iinuma, S. Kondo, K. Maeda, and H. Umezawa, *J. Antibiotics*, **28**, 613 (1975).
3. (a) S. Horii, Y. Kameda, *J. Antibiotics*, **21**, 665 (1968); (b) K. Mizuno, M. Asai, S. Horii, H. Iwasaki, and J. Ueyanagi, *Antimicrobial Agents and Chemotherapy*, **6** (1970).
4. P. A. Leclercq, L. C. Smith, and D. M. Desiderio, Jr., *Biochem. Biophys. Res. Comm.*, **45**, 937 (1971).
5. Y. Suhara, K. Maeda, and H. Umezawa, *Kasugamycin. "Deoxy Sugars"*, *Advances in Chemistry Series*, No. 74, ACS, 1968, p. 15.

6. Jerry March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, 1968, p. 319.
7. R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo, and K. Folkers, J. Am. Chem. Soc., 68, 776 (1946).
8. S. Sakaguchi, J. Biochem., 5, 25 (1925).
9. W. Konig and R. Geiger, Chem. Ber., 103, 788 (1970).

CARBOHYDRATES AS CHIRAL STARTING MATERIALS IN ORGANIC SYNTHESIS

Reported by Paula Roach

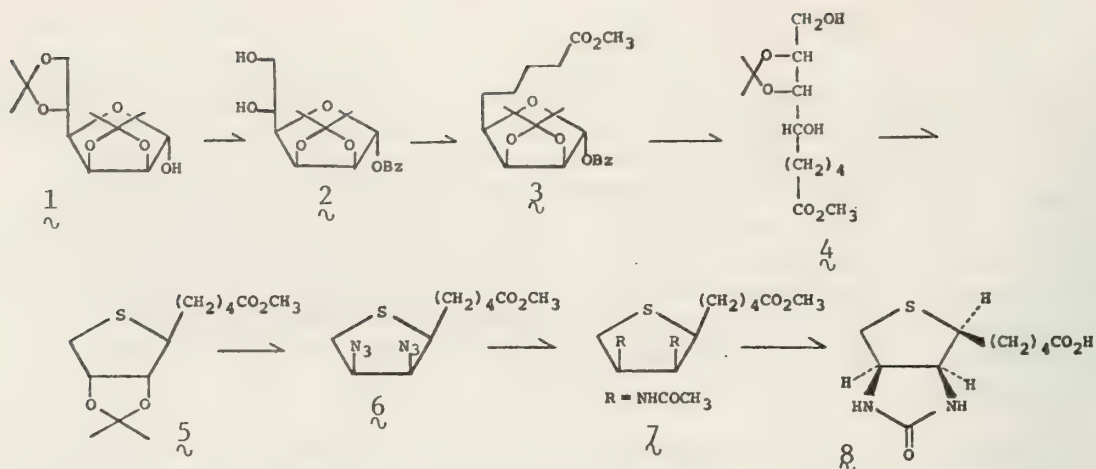
February 23, 1978

The total synthesis of natural products has always been a challenging field for the organic chemist. Not only must the carbon skeleton be made, but the correct stereochemistry at every chiral center must be achieved. In recent years, several workers have found a unique solution to this problem. By employing readily available carbohydrates as starting materials, a number of optically active centers can easily be introduced with a minimum or, in some cases, absence of requisite chromatographic separation of isomers. This seminar will describe recent synthetic efforts that have used sugars as starting materials to make non-carbohydrate natural products.

Although the overall synthetic strategy is planned in the same manner as in any organic synthesis, there are several differences that must be taken into account: (1) The selection of the starting sugar is of prime importance. Since there are many readily available carbohydrates and many ways of adding and removing functional groups from sugars, it is possible to select a starting material that either has the same chirality or can be easily converted to the stereochemistry of the target molecule. (2) If many chiral centers are involved, reactions must be stereospecific. Reactions are usually selected which conserve the configurational integrity of the starting material, for example, certain functional group transformations, which change the configuration in a predictable manner, as in S_N2 displacements, or which use the stereochemistry at one chiral center to direct or induce known stereochemistry at another position, as in Claisen rearrangements. (3) Protecting groups must be chosen that can be added and removed easily and in the proper sequence. Several workers have developed special blocking groups that are stable to a variety of conditions that would be encountered in a complete synthesis.¹ The utilization of sugars also offers advantages such as availability in optically active form, a high degree of crystallinity, and minimization of chromatography required. Workers have applied sugars to the synthesis of natural products with such varied ring structures as furans,^{2a,b,3a} pyrans, pyrones and pyrroles,^{25a,b} cyclohexane derivatives,⁴ acetals,^{5a,b} dilactones,^{6a-d} thiophenes,⁷ ureas,⁸ prostaglandins,^{9a-f} and macrolides.¹⁰ In many cases, these were the first syntheses of the natural products in optically active form.

Ohrui, Kuzuhara, and Emoto have synthesized (+)-biotin,⁷ (+)-oxy-biotin,^{3a,b} and (+)-desthiobiotin.⁸ Common to all three syntheses were introduction of the side chain by Wittig reaction on the C-5 aldehyde, S_N2 displacement of both tosylates with azide, catalytic reduction of the azide groups, and treatment with phosgene to form the urea functionality. Since azide groups are destroyed under Wittig conditions, the side chain was added either before they were introduced or after they had been reduced and protected. Ogawa, Kawano, and Matsui recently reported a synthesis of biotin from D-glucose¹¹ which employs the same elements mentioned above. Ohrui's starting material for (+)-biotin was the blocked mannofuranose 1¹² which already contains the three desired chiral centers (Scheme I). Benzoylation at C-1 followed by removal of the 5,6-O-isopropylidene group gave a 5,6-diol, 2. The side chain was added by these steps: periodic acid oxidation to the aldehyde, Wittig reaction, and hydrogenolysis to the lyxofuranate 3. Treatment with base and reduction with sodium borohydride yielded the straight chain ester 4, which was

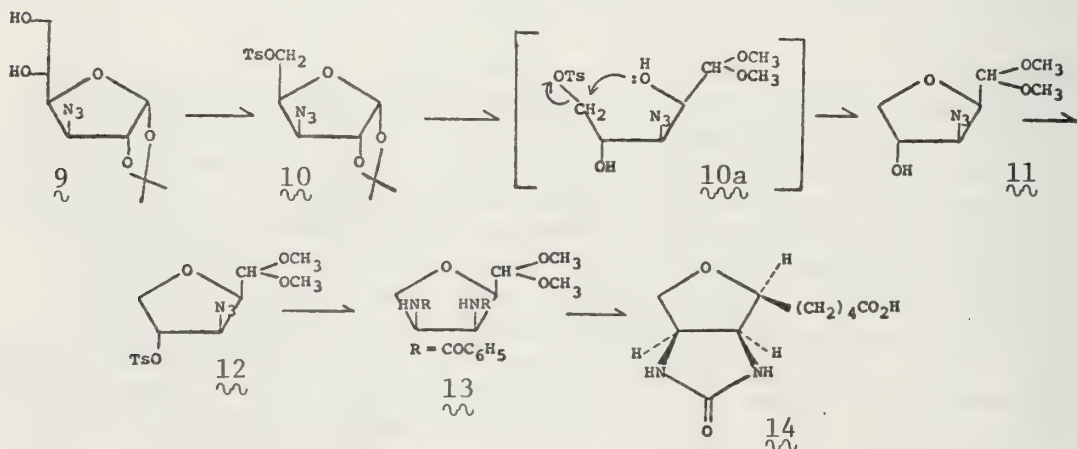
Scheme I



dimesylated and treated with sodium sulfide in HMPA to give the tetrahydrothiophene derivative 5, wherein the masked diol is set up for $\text{S}_{\text{N}}2$ inversion. Removal of the isopropylidene group, dimesylation and reaction with sodium azide produced the diazide compound 6 with correct stereochemistry. Hydrogenation over PtO_2 in methanol and acetic anhydride gave the diamide 7 which, after hydrolysis with barium hydroxide and treatment with phosgene, afforded (+)-biotin (8).

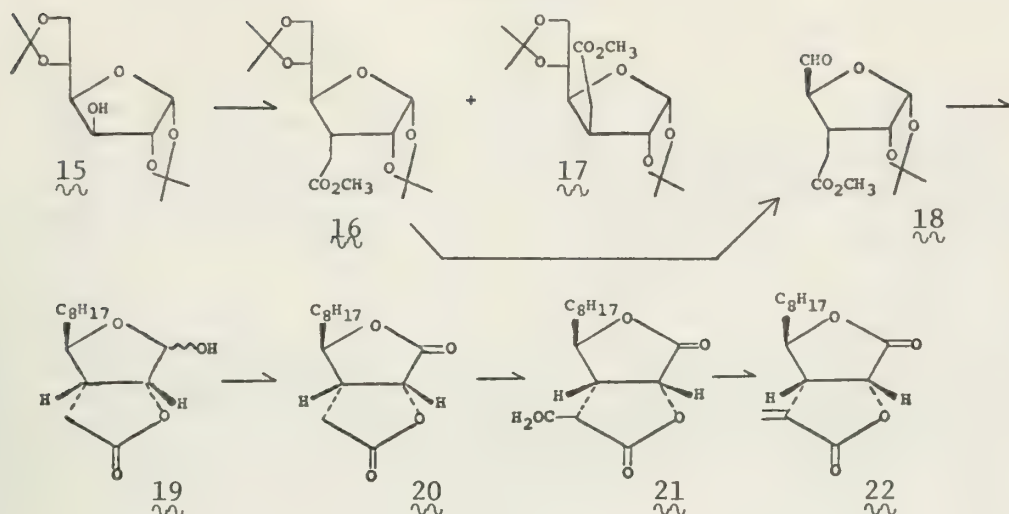
In the synthesis of (+)-oxybiotin (Scheme II), Ohrui utilized an intramolecular $\text{S}_{\text{N}}2$ reaction to form the tetrahydrofuran ring. He started with the blocked glucufuranose 9, which was formed by reactions with the 3-tosylate of allose.¹³ Periodate oxidation yielded the aldehyde which was immediately reduced with sodium borohydride and tosylated to give the xylofuranose 10. This underwent smooth rearrangement in methanolic hydrogen chloride to give the tetrahydrofuran derivative 11. The second azido group was now introduced by displacement of the C-4 tosylate 12. Reduction with zinc dust in aqueous DMF and dibenzoylation gave the 2,5-anhydro-3,4-dibenzamido-3,4-dideoxy-arabinose dimethyl acetal 13. The side chain and urea groups were added as before⁷ to give (+)-oxybiotin (14).

Scheme II



Anderson and Fraser-Reid and the Ohrui group reported independently the same synthesis of the antifungal agent (-)-avenaciolide (22)^{6a,b} (Scheme III). Their starting material was the protected diacetone

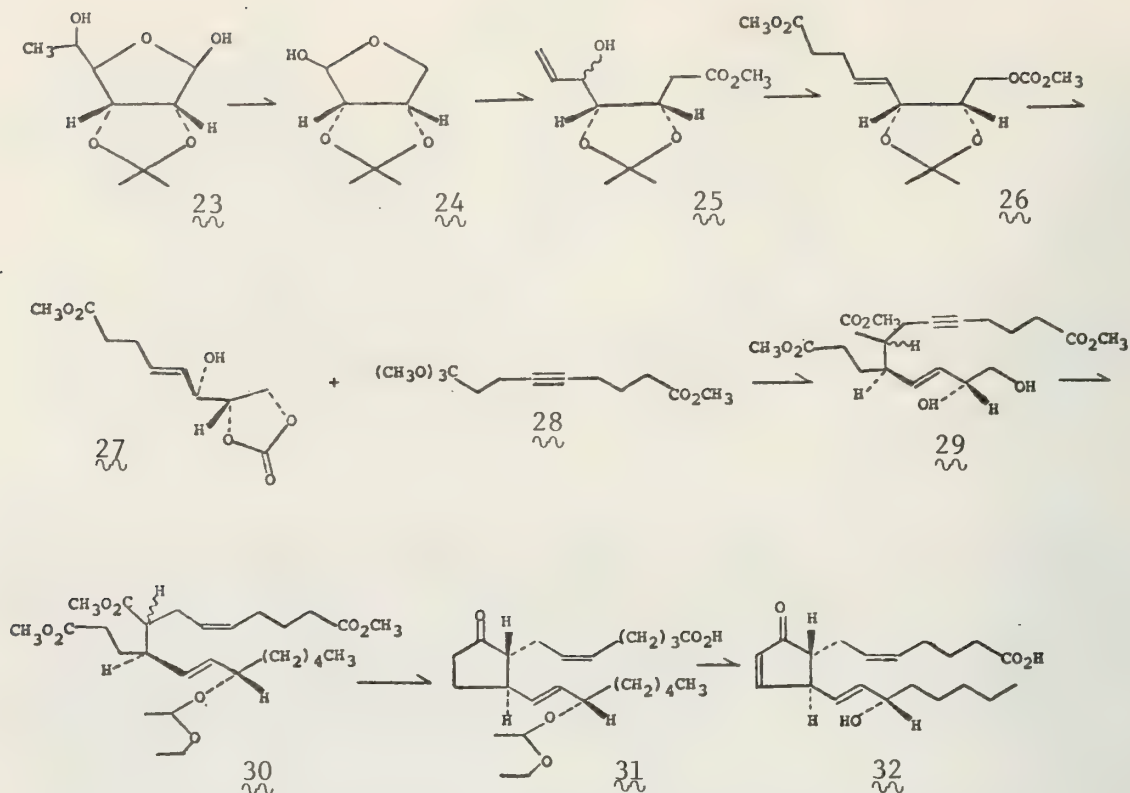
Scheme III



glucose 15.¹⁴ This contains two of the asymmetric centers of avenaciolide, a potential lactone masked as the acetal, and two sites that can be elaborated to give the side chain and second lactone. Oxidation at C-3 of 15¹⁵ followed by Wittig reaction and hydrogenation gave a mixture of allofuranose 16 and glucofuranose 17 derivatives. Selective hydrolysis of the 5,6-O-isopropylidene group of 16 and periodate oxidation gave the aldehyde 18. The side chain was introduced via Wittig reaction and subsequent hydrogenation over palladium on carbon. Treatment with acid effected both hydrolysis of the 1,2-O-isopropylidene group and lactonization to the hemiacetal 19. Jones reagent oxidized the hemiacetal to the lactone 20, and the methylene group was introduced according to the procedure of Parker and Johnson:¹⁶ carboxylation with methyl magnesium carbonate¹⁷ to give 21 and treatment with diethylamine, formaldehyde¹⁸ and acetic acid to yield (-)-avenaciolide (22).

Sugars were utilized by Stork in his syntheses of PGA₂,^{9a} PGE₁,^{9b} and, most recently, PGF₂.^{9c} Since the synthesis of PGF₂ was done with chemistry from the earlier two syntheses, only those will be discussed here. Stork chose as starting material for PGA₂ (32) (Scheme IV) the masked erythrose 24, which was synthesized from the rhamnose derivative 23 by reduction of the C-1 aldehyde and oxidation with periodate to the C-4 aldehyde.¹⁹ This precursor was to be elaborated further to an allylic alcohol which could undergo Claisen rearrangement to form the trans double bond. The stereochemistry at the acetonide was crucial, for the C-2 hydroxyl was to become the C-15 (prostaglandin numbering) alcohol of PGA₂, and the C-3 hydroxyl was to direct the second Claisen rearrangement which determines the C-12 (prostaglandin numbering) side chain stereochemistry. Reaction of 24 with vinyl magnesium chloride and protection of the primary alcohol as the methyl carbonate yielded the vinyl carbinol 25. Claisen rearrangement with trimethyl orthoacetate gave the γ,δ -unsaturated ester 26. Since an allylic alcohol was again required, it was necessary to mask selectively the C-1, C-2-diol. Hydrolysis removed the isopropylidene group, and treatment with triethylamine produced the allyl alcohol 27. Claisen rearrangement with the orthoester 28 followed by hydrolysis gave the diol 29 as a mixture, epimeric at the side chain as shown. Since this would be epimerized later, the mixture was carried on. An n-pentyl group was substituted for the primary alcohol as follows: the triple bond was reduced over palladium-barium sulfate to the cis double bond, the secondary hydroxyl was protected as the ethyl vinyl ether, and the primary alcohol was tosylated and displaced with lithium dibutyl-

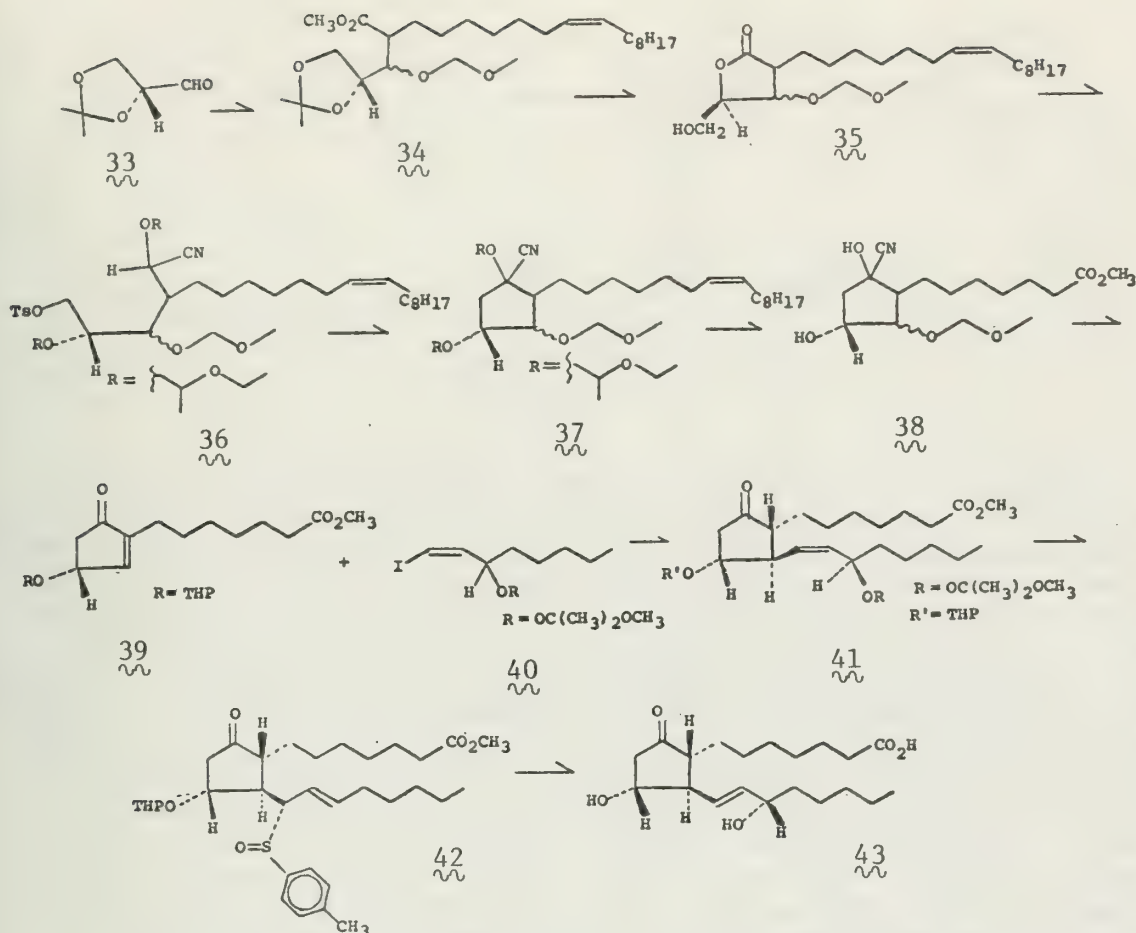
Scheme IV



cuprate to give the triester 30. Cyclization, hydrolysis, and acidification yielded the acid 31 in which epimerization to the correct isomer had occurred. Selenation at the α -keto position followed by periodate oxidation introduced the α,β -unsaturation. Hydrolysis of the ethoxyethyl group produced PGA₂ (32).

Stork approached the synthesis of PGE₁ (43) in a different manner (Scheme V). The starting material was the isopropylidene derivative of D-glyceraldehyde 33. The C-2 hydroxyl became the C-11 hydroxyl of PGE₁, and the aldehyde was used for chain extension. The other optical and geometric problems were resolved by the application of stereospecific reactions. The protected glyceraldehyde 33 was condensed with the anion of methyl oleate and the resulting secondary alcohol was protected with chloromethyl methyl ether to give the aldol 34. Methyl oleate was the reagent of choice because oxidation of the double bond to the acid would give the C-8 prostaglandin side chain with the correct number of carbons. The mixed acetal of formaldehyde was used as a protecting group because of its stability to subsequent acidic conditions. After removal of the isopropylidene protecting group, lactonization afforded the γ -lactone 35. This was converted to the tosylate, reduced with DIBAL to the cyclic hemiacetal, and treated with hydrogen cyanide to give the cyanohydrin 36, after protection of the hydroxyl groups with ethyl vinyl ether. The related acyl carbanion equivalent could attack the tosylate to effect ring closure. As a protected aldol system, stable to mild acid, oxidation of the side chain could be accomplished without destroying the cyclopentane ring. The masked cyclopentane 37 was isolated after 36 was heated at reflux with sodium hexamethylsilazane. Oxidation to the carboxylic acid was accomplished with sodium periodate-potassium permanganate; aqueous acid regenerated the hydroxyl groups, and treatment with diazomethane produced the cyanohydrin ester 38.

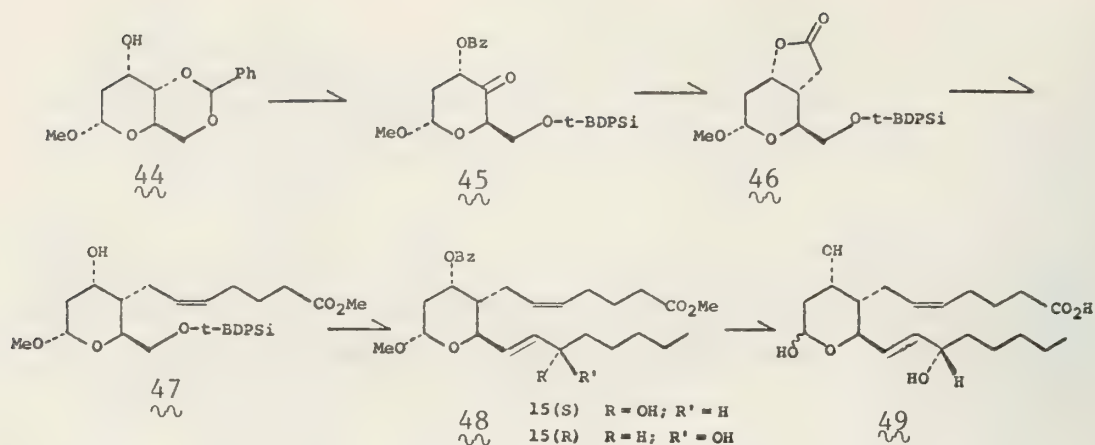
Scheme V



Reaction with cold sodium hydroxide followed by cold hydrochloric acid gave the cyclopentenone 39. This was a crucial intermediate since addition of the C-12 side chain by reaction of 39 with the lithium cuprate of the vinyl iodide 40 was expected to be stereospecific.²¹ Kluge, Untch, and Fried noted that (+)-39 reacted much faster with the (R) isomer of 40 than the (S) isomer to give an 86:14 ratio in favor of the desired epimer 41.²⁰ Stork extended this by causing (+)-39 to react with (±)-40 and obtaining 41 completely free of the unwanted isomer. At this point, there still remained the isomerization of the cis double bond to trans, and the inversion of configuration at the C-15 hydroxyl group. This was all accomplished by forming the aryl sulfenate ester at C-15 of 41 which undergoes a [2,3] sigmatropic rearrangement to the sulfoxide 42.²¹ Treatment with trimethyl phosphite²¹ and removal of all protecting groups gave PGE₁ (43).

Several prostaglandin derivatives have also been synthesized from carbohydrates. Hanessian has synthesized 11-oxy prostaglandins from 1,4-anhydroglucitol.^{2a} Thromboxane B₂ (TBX₂) (49), a six-membered hemiacetal formed along with prostaglandins in some cells, has been synthesized independently by Hanessian,^{9d} Hernandez,^{9f} and Corey.^{9e} Hernandez and Corey reported very similar syntheses starting with D-glucose and utilizing the orthoester Claisen rearrangement to introduce the C-9 (prostaglandin numbering) configuration. Hanessian began with the 2-deoxyribohexanose 44 (Scheme VI), which was synthesized from 4,6-O-benzylidene-D-glucose by

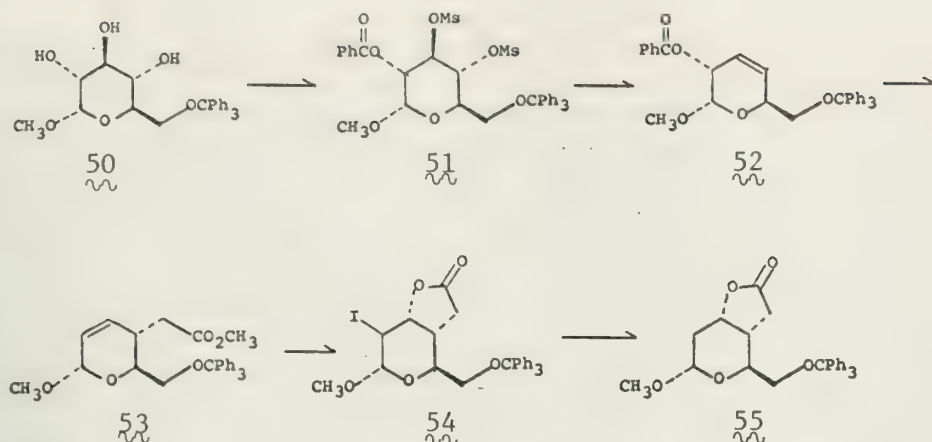
Scheme VI



ditosylation of the C-2 and C-3 hydroxyl groups, treatment with sodium methoxide to form the epoxide, and reduction with lithium aluminum hydride to the 2-deoxy compound with inverted configuration at C-3. This compound already contained the basic ring structure of TBX₂ and the three chiral centers of correct configuration. All that was needed was the stereo-specific introduction of the side chains since the C-9 alcohol function needed only to be protected. Hydrogenation of ribohexanose **44**, protection of the primary alcohol as a t-butyldiphenylsilyl ether¹ (stable to acid and hydrogenation conditions) and oxidation with EDAC·HCl afforded the 4-uloside derivative **45**. Wittig reaction, hydrogenation over palladium oxide and treatment with base yielded the lactone **46**. Reduction with DIBAL, Wittig reaction, and esterification with diazomethane gave the hydroxy ester **47**. This was oxidized to the ketone and treated with potassium carbonate in methanol. No equilibration of the α side chain occurred, confirming that the C-3, C-4 cis stereochemistry had been introduced by hydrogenation. The C-3 hydroxyl of **47** was protected with benzoyl chloride and the t-butyldiphenylsilyl ether was removed with n-butylammonium fluoride. Collins oxidation and Wittig reaction²² gave an α,β-unsaturated ketone which was reduced with zinc borohydride to a mixture of C-15 epimeric alcohols **48**. Chromatographic separation afforded the 15(S) isomer which, after hydrolysis, gave TBX₂ (**49**).

Hernandez and Corey also started with D-glucose, but instead, used a series of stereospecific reactions to achieve the 2-deoxy-3,4-cis stereochemistry (Scheme VII). Selective benzylation at C-2 of the glycoside **50** was possible by treatment with di-n-butyltin oxide followed by benzoyl chloride. Reaction with methanesulfonyl chloride yielded the dimesylate **51** which, after treatment with potassium iodide, zinc-copper couple, and base, afforded the allylic alcohol **52**. Claisen rearrangement with trimethyl orthoacetate gave the unsaturated ester **53** which then had the correct side chain configuration. Introduction of the C-9 hydroxyl group was achieved by treatment of **53** with potassium iodide-iodine in aqueous sodium bicarbonate and hydrolysis to the γ-lactone **54**. Removal of the iodine with tri-n-butyltin hydride afforded the protected lactone **55** which, excepting the C-6 protecting group, is identical to the lactone **46** synthesized by Hanessian. Final conversion to TBX₂ (**49**) was done as above according to the procedure of Corey, *et al.*²²

Scheme VII



The most elegant synthesis with carbohydrates attempted so far is that of erythronolide A (65)¹⁰ (Figure 1). Hanessian recognized in the C₁₄ macrolide two functionalized sugar derivatives connected by a two-carbon bridge and a lactone bond. He has developed a highly efficient synthetic plan by which he synthesized two precursors which correspond to the two halves of the erythronolide A. Since precursor I has L-ido stereochemistry and precursor II has D-gluco stereochemistry, each precursor could be developed from one common intermediate prepared from D-glucose. The equatorial C-2 methyl and C-3 hydroxyl were common to both precursors; however, precursor I had

Scheme VIII

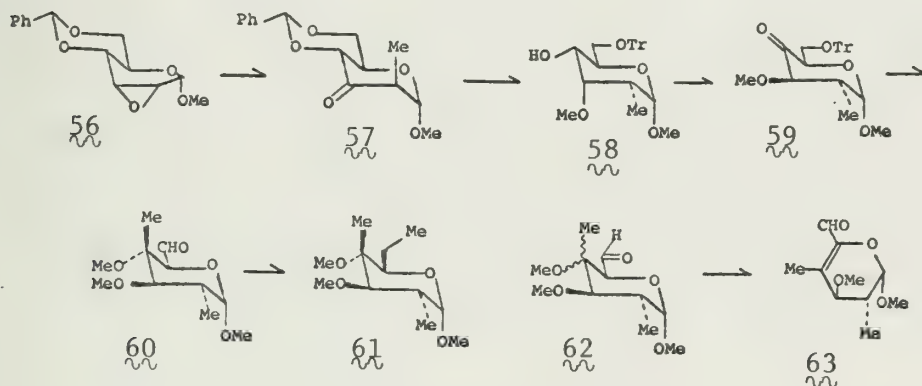
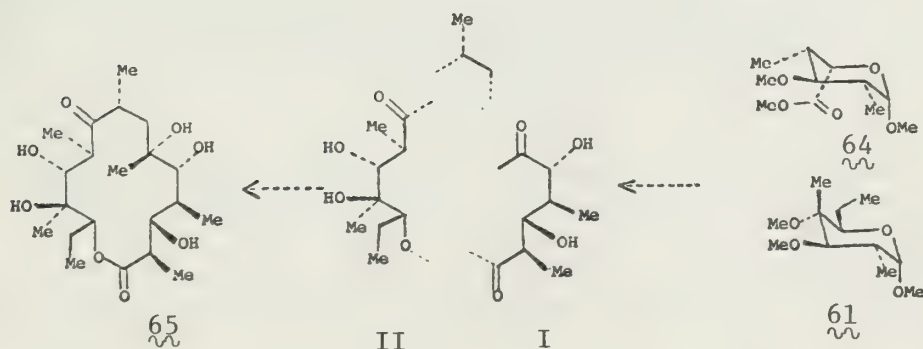


Figure 1



an additional deoxy methyl and axial side chain. Therefore, the 4-uloside 59 which already contains the proper C-2 and C-3 stereochemistry was the first synthetic target (Scheme VIII).

Hanessian started with D-glucose which, after protection with benzaldehyde, was ditosylated and treated with sodium methoxide to form the epoxide 56. Reaction with lithium dimethylcuprate introduced an axial methyl group at C-2. Oxidation with DMSO produced the 3-uloside 57 which, upon treatment with sodium methoxide, equilibrated completely to the more stable equatorial isomer. Sodium borohydride reduction, methylation of the axial alcohol and replacement of the 4,6-O-benzylidene group with a 6-trityl group gave the tritylated derivative 58. Oxidation at C-4 was accomplished with DMSO-EDAC·HCl, and treatment again with sodium methoxide gave the common intermediate 59. To obtain precursor II, a C-6 ethyl group and C-4 axial methyl and equatorial hydroxyl group were required. Reaction of 59 with methyllithium produced a mixture of epimers in which the main isomer had the C-4 methyl group axial; after methylation, the two isomers could be separated by fractional crystallization. Removal of the trityl group and Collins oxidation yielded the aldehyde 60. Introduction of a methylene group by Wittig reaction and subsequent hydrogenation afforded 61, which is the dimethylated derivative of precursor II.

To obtain precursor I, an equatorial methyl group and cis C-5 ester side chain were needed. The cis geometry could be achieved by hydrogenation of an unsaturated intermediate which was prepared from the mother liquors of the methyllithium reaction on 59. This mixture of epimers was detritylated and oxidized with Collins reagent to the aldehyde 62. Dilute aqueous calcium hydroxide effected the conversion to the α,β -unsaturated aldehyde 63. Base-catalyzed conditions produced a mixture of exo and endo unsaturated compounds. Eliminations employing a C-5 ester group and either an axial or equatorial hydroxyl group also gave mixtures; attempts at double bond migration were unsuccessful. The aldehyde 63 was oxidized with manganese dioxide, sodium cyanide, acetic acid, and methanol to the α,β -unsaturated ester. This was hydrogenated over palladium on carbon to precursor I 64. The C-5 ester side chain stereochemistry was confirmed by NMR and by a synthesis of a C-5-keto idofuranose which equilibrated to the gluco epimer. With both precursor I and II in hand, there still remain lactonization and connection of the two halves via a two-carbon bridge containing the last methyl group. Although two more optical centers must be introduced, the stereospecific synthesis, without chromatography, of precursors with eight chiral centers is in itself a landmark achievement.

Other chiral syntheses with carbohydrates are now in progress. Gigg and Conant have begun a synthesis of sphingosine,^{23a,b} and Miljkovic has done work on possible macrolide precursors.²⁴ As the utility of the sugars becomes better known, we can expect further significant contributions to the total synthesis of asymmetric natural products.

BIBLIOGRAPHY

1. S. Hanessian and P. Lavallee, *Can. J. Chem.*, 53, 2975 (1975).
2. (a) S. Hanessian, P. Dextraze, A. Fougere, and Y. Guidon, *Tetrahedron Lett.*, 3983 (1974); (b) G. J. Lourens and J. M. Koekemoer, *Tetrahedron Lett.*, 3715 (1975).
3. (a) H. Ohru, H. Kuzuhara, and S. Emoto, *Agr. Biol. Chem.*, 34, 375 (1970); (b) H. Ohru, H. Kuzuhara, and S. Emoto, *ibid.*, 35, 752 (1971).

4. S. Ogawa, K. Rinehart, Jr., G. Kimura, and R. P. Johnson, *J. Org. Chem.*, 39, 812 (1974).
5. (a) H. Ohruai and S. Emoto, *Agr. Biol. Chem.*, 40, 2267 (1976); (b) D. R. Hicks and B. Fraser-Reid, *J. Chem. Soc. Chem. Commun.*, 869 (1976).
6. (a) R. C. Anderson and B. Fraser-Reid, *J. Am. Chem. Soc.*, 97, 3870 (1975); (b) H. Ohruai and S. Emoto, *Tetrahedron Lett.*, 3657 (1975); (c) S. Kusumoto, S. Tsuji, and T. Shiba, *Bull. Chem. Soc. Japan*, 47, 2690 (1974); (d) A. Aburaki and M. Kinoshita, *Chem. Lett.*, 701 (1976).
7. H. Ohruai and S. Emoto, *Tetrahedron Lett.*, 2765 (1975).
8. H. Kuzuhara, H. Ohruai, and S. Emoto, *Agr. Biol. Chem.*, 35, 8 (1971).
9. (a) G. Stork and S. Raucher, *J. Am. Chem. Soc.*, 98, 1583 (1976); (b) G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, 99, 1275 (1977); (c) G. Stork, private communication; (d) S. Hanessian and P. Lavallee, *Can. J. Chem.*, 55, 562 (1977); (e) E. J. Corey, M. Shibasaki, and J. Knolle, *Tetrahedron Lett.*, 1625 (1977); (f) O. Hernandez, *Tetrahedron Lett.*, 219 (1978).
10. S. Hanessian and G. Rancourt, *Pure and Appl. Chem.*, 49, 1201 (1977).
11. T. Ogawa, T. Kawano, and M. Matsui, *Carbohydr. Res.*, 57, C31 (1977).
12. K. Freudenberg and A. Wolf, *Chem. Ber.*, 60, 232 (1927).
13. W. M. zu Reckendorf, *Chem. Ber.*, 101, 3802 (1968).
14. O. T. Schmidt, *Methods Carbohydr. Chem.*, 2, 230 (1963).
15. H. Paulsen, W.-P. Trautwein, F. G. Espinosa, and K. Heyns, *Chem. Ber.*, 100, 2822 (1967).
16. W. L. Parker and F. Johnson, *J. Org. Chem.*, 38, 2489 (1973).
17. H. L. Finkbeiner and M. Stiles, *J. Am. Chem. Soc.*, 85, 616 (1963).
18. E. E. van Tamelen and S. R. Bach, *J. Am. Chem. Soc.*, 77, 4683 (1955).
19. J. N. Baxter and A. S. Perkin, *Can. J. Chem.*, 38, 2217 (1960).
20. A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, 94, 9256 (1972).
21. J. G. Miller, W. Kurz, K. G. Untch, and G. Stork, *J. Am. Chem. Soc.*, 96, 6774 (1974).
22. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.*, 92, 397 (1970).
23. (a) R. Gigg and R. Conant, *J. Chem. Soc. Perkin I*, 2006 (1977); (b) P. Gent, R. Gigg, and R. Conant, *ibid.*, 248 (1972).
24. M. Miljkovic, M. Gligorijevic, T. Satoh, and D. Miljkovic, *J. Org. Chem.*, 39, 1379 (1974).
25. (a) K. Olsson, P. Pernemuln, T. Popoff, and O. Theander, *Acta Chem. Scand.*, B31, 469 (1977); (b) E. Fischer and F. W. Lichtenthaler, *Angew. Chem.*, 86, 590 (1974).

THE CHEMISTRY OF ENAMIDES

Reported by Linda G. Carter

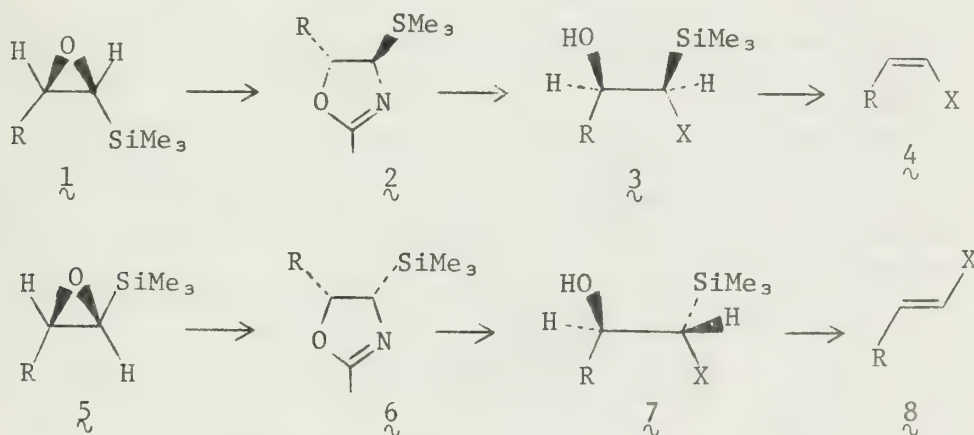
February 27, 1978

The chemistry of enamides, $R-CO-N(R^1)CR^2=CR^3R^4$, also referred to as N-acylenamines and N-vinylamides, until recently has received little consideration. The simple enamides have been shown to be rather unstable, polymerizing readily in the presence of light, heat, or acidic media to afford polyvinylamides.¹ In the last decade, enamides have exhibited industrial importance, functioning as precursors to some plastics, cosmetics, and pesticides.^{1,2} Moreover, the biochemical importance^{1,3} of these compounds as intermediates in the syntheses of many polycyclic natural products has been appreciated.⁴

The instability of the enamides is such that no truly general syntheses are available, only specifically applicable ones. Industrially, an enamide is generally prepared by the condensation of an amide and an alkyne, under conditions of high temperature and pressure and catalysis by an alkali metal.^{1,2} Many acyclic primary N-vinylamides can be synthesized via reaction of an amide and an aldehyde in an acidic medium to afford an enamide and/or an alkylidenebisamide.⁵ The latter can be thermally decomposed to form the corresponding enamide.⁶ Ketones are generally unreactive under these conditions,⁷ but secondary N-vinylamides can occasionally be prepared via alkylation of a primary N-vinylamide.⁸ Deacylation or dehydration of certain N- β -acyl- or hydroxy-alkyl secondary amides at elevated temperature can also afford secondary N-vinylamides.¹

The synthetic methods described above give mixtures of stereoisomers; accordingly, separation of the isomers is required. A recent communication of Hudrlik and co-workers⁹ provides the first stereospecific synthesis of enamides. In that case, α,β -epoxysilanes, **1** and **5**, are allowed to react with acetonitrile in the presence of boron trifluoride etherate to give 5-silyloxazolines, **2** and **6**. Hydrolysis of the oxazolines yields hydroxyamides, **3** and **7**, which eliminate to give enamides, **4** and **8**, in isomeric purities over 99%.

Scheme I

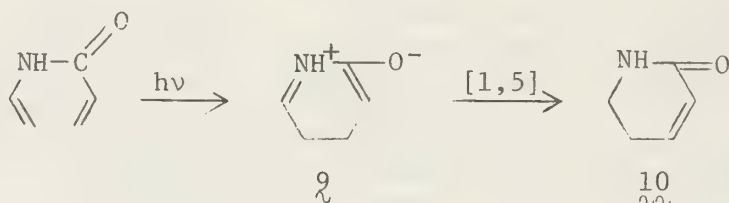


$R = n\text{-C}_6\text{H}_{13}$; $X = \text{NHAc}$

In specific cases, more complex enamides have been synthesized from oxazolines,¹⁰ ketoximes,^{3,11} iminoketones,¹² *o*-trimethylsilyl lactams,¹³ olefin-palladium (II)chloride complexes,¹⁴ nitriles,¹⁵ ynamides,¹⁶ and imines.¹⁷

Enamides upon photolysis give such nitrogen-heterocyclic compounds as isoquinoline alkaloids.^{3,4} Initially, N-alkyl and some N-aryl acyl-enamines were thought to give only [1,3] acyl shifts, upon photolysis, leading to vinylogous amides.¹⁸ More recently, enamides with unsaturation α,β to the carbonyl were found to undergo photocyclization to give such natural products as crinan, aporphine, and yohimbine alkaloids.^{3,4,19-25} This photocyclization is envisioned to proceed via an aza analogue of a hexatriene-cyclohexadiene photocyclization to form an intermediate, **9**, which undergoes a [1,5] hydrogen shift to afford **10**, as indicated in Scheme II. Both stereospecific and nonstereospecific cases have been reported.^{3,4,20-25}

Scheme II



Other conversions of certain enamides have been investigated, including hydrolysis,²⁴ reduction,²⁴ and bromination.²⁵ These reactions along with the photolytic ones are suggestive of further potential application for enamide chemistry.

BIBLIOGRAPHY

1. C. E. Schildnecht, "Vinyl and Related Polymers", New York, Wiley and Sons, 1952.
2. (a) Ger. Patent 1,245,939, CA 69: P49117m; (b) Ger. Patent 1,228,246, CA 66: 28403v; (c) U.S. Patent 3,296,126, CA 66: 87326v; (d) Brit. Patent 857,754, CA 55: 15909f; (e) Belg. Patent 634,033, CA 61: P4227f.
3. I. Ninomiya, T. Naito, and T. Kiguchi, *Tetrahedron Lett.*, 4551 (1970).
4. I. Ninomiya, *Heterocycles*, 2, 105 (1974).
5. (a) J. Zabicky (ed.), "The Chemistry of Amides", London, Wiley and Sons, 1970, p. 758; (b) F. Eiden, *Angew Chem., Int. Ed. Engl.*, 6, 377 (1967).
6. D. Ben-Ishai and R. Giger, *Tetrahedron Lett.*, 4523 (1965).
7. U. Zehavi and D. Ben-Ishai, *J. Org. Chem.*, 26, 1097 (1961).
8. R. B. Boar, J. F. McGhie, M. Robinson, D. H. R. Barton, D. C. Horwell, and R. V. Stick, *J. Chem. Soc., Perkin I*, 1237 (1975) and references within.
9. P. F. Hudrlik, A. M. Hudrlik, R. J. Rona, R. N. Misra, and G. P. Withers, *J. Am. Chem. Soc.*, 99, 1993 (1977).
10. W. L. Salo and H. G. Fletcher, Jr., *J. Org. Chem.*, 34, 3189 (1969).
11. R. B. Boar, J. F. McGhie, M. Robinson, and D. H. R. Barton, *J. Chem. Soc., Perkin I*, 1242 (1975).
12. (a) D. Y. Curtin and J. E. Richman, *Tetrahedron Lett.*, 3081 (1969); (b) D. Y. Curtin and J. H. Engelmann, *ibid.*, 3911 (1968).
13. H. Kaye and S.-H. Chang, *Tetrahedron*, 1369 (1970).
14. H. Hirai and H. Sawai, *Bull. Chem. Soc., Japan*, 43, 2208 (1970).
15. (a) U. Schöllkopf, R. Schröder, and E. Blume, *Ann. Chem.*, 766, 130 (1972); (b) U. Schöllkopf and R. Schröder, *Angew. Chem., Int. Ed. Engl.*, 11, 311 (1972).

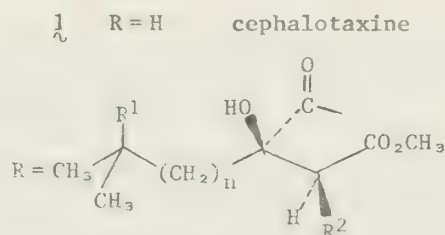
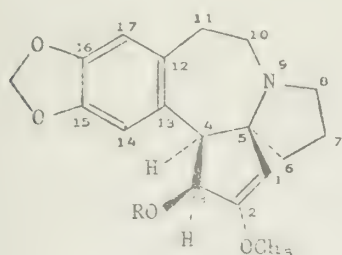
16. E. Goffin, Y. Legrand, and H. C. Viehe, J. Chem. Res. (M), 1165 (1977) and references within.
17. J. P. Chupp and E. R. Weiss, J. Org. Chem., 33, 2357 (1968).
18. (a) N. C. Yang and G. R. Lenz, Tetrahedron Lett., 4897 (1967); (b) R. W. Hoffman and K. R. Eicken, *ibid.*, 1759 (1968); (c) R. W. Hoffman and K. R. Eicken, Chem. Ber., 102, 2987 (1969).
19. G. R. Lenz, Tetrahedron Lett., 1963 (1973).
20. (a) I. Ninomiya, T. Naito, and T. Mori, J. Chem. Soc., Perkin I, 505 (1973); (b) I. Ninomiya, T. Naito, and T. Mori, Tetrahedron Lett., 2259 (1969); (c) I. Ninomiya, T. Naito, and T. Kiguchi, J. Chem. Soc., Perkin I, 2257 (1973); (d) I. Ninomiya, T. Naito, and T. Kiguchi, *ibid.*, 2261 (1973).
21. P. S. Mariano, E. Krochmal, Jr., and A. Leone, J. Org. Chem., 42, 1122 (1977).
22. (a) G. R. Lenz, J. Org. Chem., 39, 2839 (1974); (b) G. R. Lenz, *ibid.*, 39, 2846 (1974); (c) G. R. Lenz, *ibid.*, 42, 1117 (1977).
23. G. R. Lenz, J. Org. Chem., 41, 2201 (1976).
24. (a) A. Brossi, J. Wuersch, and O. Schneider, Chimia, 12, 114 (1958); (b) I. Baxter and G. A. Swan, J. Chem. Soc., Sect. C, 4014 (1965).
25. (a) I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, J. Chem. Soc., Perkin I, 1696 (1973); (b) T. Kametani, T. Sugai, Y. Shoji, T. Honda, F. Satoh, and K. Fukumoto, J. Chem. Soc., Perkin I, 1151 (1977).

SYNTHESIS OF CEPHALOTAXUS ALKALOIDS: AZA-SPIRO COMPOUNDS

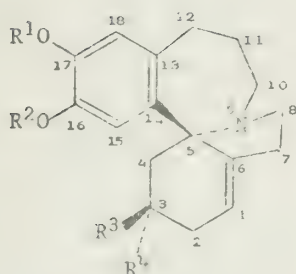
Reported by Susan L. Wells

March 2, 1978

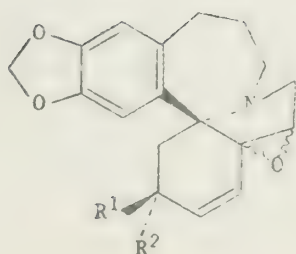
Cephalotaxine (1) is the major alkaloid from the plant genus Cephalotaxus (plum-yews).¹ Several naturally occurring esters of cephalotaxine (2 - 5) have potent anti-tumor properties against leukemia in mice, although neither cephalotaxine nor the diacid side chains are active by themselves.^{1,2} The molecular basis for the biological activity of the cephalotaxine esters is unknown, but recent studies have indicated that these compounds block the initiation of protein synthesis.³ Recently, small amounts of biogenetically related⁴ homoerythrina (Schelhammera) alkaloids (6 - 12) have been isolated from species of Cephalotaxus.^{1a,b} Biosynthetic studies of cephalotaxine by Parry indicate that tyrosine and phenylalanine are incorporated into the molecule in an unusual manner.^{4c,d,f} The diacid side chains appear to be a straightforward modification of amino acid biosynthesis.^{4e}



	R ¹	R ²	n	
<u>2</u>	OH	H	2	harringtonine
<u>3</u>	H	OH	2	isoharringtonine
<u>4</u>	OH	H	3	homoharringtonine
<u>5</u>	H	H	2	deoxyharringtonine



	R ¹	R ²	R ³	R ⁴
<u>6</u>	CH ₃	H	OCH ₃	H
<u>7</u>	CH ₃	CH ₃	OCH ₃	H
<u>8</u>		-CH ₂ -	H	OCH ₃
<u>9</u>	CH ₃	H	H	OCH ₃
<u>10</u>	CH ₃	CH ₃	H	OCH ₃



	R ¹	R ²	
<u>11</u>	OCH ₃	H	wilsonine
<u>12</u>	H	OCH ₃	3- <u>epi</u> -wilsonine

The structures and stereochemistry of cephalotaxine, originally assigned by spectral methods, have been confirmed by Bates' x-ray studies on the p-bromobenzoate^{5a} and free forms of cephalotaxine.^{5b} This work permitted assignment of the absolute configuration: the first x-ray study of cephalotaxine methiodide was ambiguous because of racemization of all four chiral centers during synthesis of the derivative.^{5c} Brandänge's group used CD studies to assign the absolute configurations of the diacid side chains in the ester.⁶

Synthetic studies of the cephalotaxine system are due in large part to its medical interest and meager availability from natural sources. The first syntheses of cephalotaxine were accomplished independently by Weinreb^{7,8} and Semmelhack.^{7,9} Alternative routes to major synthons have also been published.¹⁰ While the diacid side chains have been synthesized separately,¹¹ esterification has proved to be a non-trivial problem, presumably because of steric hindrance. This difficulty has been overcome for deoxyharringtonine by elaboration of the acid after esterification of a precursor to cephalotaxine.¹² Mikolajczak, Smith, and Powell have synthesized a variety of cephalotaxine esters with the objective of finding one with acceptable biological activity and simpler synthesis.²

Several groups are investigating syntheses of related alkaloid skeletons,¹³⁻¹⁷ such as homoerythrina alkaloids,¹⁴ and other azaspiro compounds,¹⁵ including histrionicotoxin¹⁶ and serratinine.¹⁷

BIBLIOGRAPHY

1. Two reviews of Cephalotaxus alkaloids with references on isolation, structure identification, and biological aspects have been published: (a) J. A. Findlay, *Int. Rev. Sci.: Org. Chem.*, Ser. Two, 9, 23 (1976); (b) C. R. Smith, Jr., R. G. Powell, and K. L. Mikolajczak, *Cancer Treat. Rep.*, 60, 1157 (1976). A wider review of all anticancer compounds isolated from plants has appeared: (c) G. A. Cordell and N. R. Farnsworth, *Lloydia*, 40, 1 (1977).
2. For leading references on the antitumor screening and activity of these compounds, see K. L. Mikolajczak, C. R. Smith, Jr., and D. Weisleder, *J. Med. Chem.*, 20, 328 (1977).
3. (a) A. P. Grollman and M. T. Huang, *Fed. Proc.*, *Fed. Am. Soc. Exp. Biol.*, 32, 1673 (1973); (b) M. T. Huang, *Mol. Pharmacol.*, 11, 511 (1975); (c) J. S. Tscherne and S. Pestka, *Antimicrob. Agents Chemother.*, 8, 479 (1975).
4. (a) V. A. Snieckus, *The Alkaloids (Specialist Periodical Report)*, 1, 149 (1971); (b) R. G. Powell, *Phytochem.*, 11, 1467 (1972); (c) A. R. Battersby, E. McDonald, J. A. Milner, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Tetrahedron Lett.*, 3419 (1975); (d) R. J. Parry and J. M. Schwab, *J. Am. Chem. Soc.*, 97, 2555 (1975); (e) R. J. Parry, D. D. Sternbach, and M. D. Cabelli, *J. Am. Chem. Soc.*, 98, 6380 (1976); (f) J. M. Schwab, M. N. T. Chang, and R. J. Parry, *J. Am. Chem. Soc.*, 99, 2368 (1977).
5. (a) S. K. Arora, R. B. Bates, R. A. Grady, and R. G. Powell, *J. Org. Chem.*, 39, 1269 (1974); (b) S. K. Arora, R. B. Bates, R. A. Grady, G. Germain, J. P. Declercq, and R. G. Powell, *J. Org. Chem.*, 41, 551 (1976); (c) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969).
6. (a) S. Brandänge, S. Josephson, and S. Vallén, *Acta Chem. Scand.*, B 28, 153 (1974); (b) S. Brandänge, S. Josephson, S. Vallén, and R. G. Powell, *Acta Chem. Scand.*, B 28, 1237 (1974).

7. S. M. Weinreb and M. F. Semmelhack, *Accounts Chem. Res.*, 8, 158 (1975). This review emphasizes the synthetic work of these two research groups.
8. (a) J. Auerbach and S. M. Weinreb, *J. Am. Chem. Soc.*, 94, 7172 (1972); (b) S. M. Weinreb and J. Auerbach, *ibid.*, 97, 2503 (1975).
9. (a) M. F. Semmelhack, B. P. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, 94, 8629 (1972); (b) M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973); (c) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, 97, 2507 (1975).
10. (a) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, 37, 3691 (1972); (b) I. Tse and V. Snieckus, *J. Chem. Soc., Chem. Commun.*, 505 (1976); (c) B. Weinstein and A. R. Craig, *J. Org. Chem.*, 41, 875 (1976).
11. (a) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, 28, 1995 (1972); (b) T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 3501 (1973); (c) T. Ipaktchi and S. M. Weinreb, *ibid.*, 3895 (1973); (d) J. Auerbach, T. Ipaktchi, and S. M. Weinreb, *ibid.*, 4561 (1973); (e) T. Utawanit, Ph.D. thesis, University of Illinois, 1975.
12. K. L. Mikolajczak, C. R. Smith, Jr., D. Weisleder, T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 283 (1974).
13. M. Lennon, A. McLean, G. R. Proctor, and I. W. Sinclair, *J. Chem. Soc., Perkin I*, 622 (1975).
14. (a) E. McDonald and A. Suksamrarn, *Tetrahedron Lett.*, 4425 (1975); (b) J. P. Marino and J. M. Samanen, *J. Org. Chem.*, 41, 179 (1976).
15. (a) T. A. Bryson and C. A. Wilson, *Syn. Commun.*, 6, 521 (1976); (b) T. A. Bryson, D. C. Smith, and S. A. Krueger, *Tetrahedron Lett.*, 525 (1977).
16. (a) M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, *J. Org. Chem.*, 40, 2009 (1975); (b) T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, *J. Org. Chem.*, 40, 2011 (1975); (c) E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.*, 97, 430 (1975).
17. (a) T. Harayama, M. Ohtani, M. Oki, Y. Inubushi, *J. Chem. Soc., Chem. Commun.*, 827 (1974); (b) T. Harayama, M. Ohtani, M. Oki, Y. Inubushi, *Chem. Pharm. Bull.*, 23, 1511 (1975).

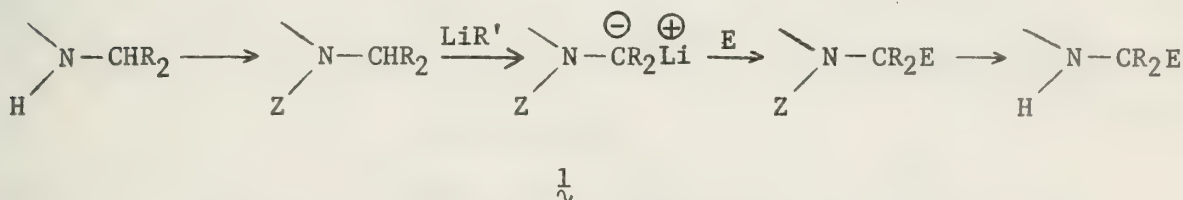
α -AZA CARBANIONS

Reported by William J. Zajdel

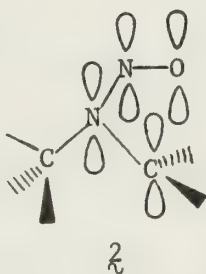
March 6, 1978

The synthetic utility and mechanistic investigation of the α -aza carbanionic synthon ($\frac{1}{\sim}$), formed by the deprotonation of a carbon atom adjacent to nitrogen, activated by some group (Z), is receiving increasing attention. If the activating group can be added and removed readily, as shown in Scheme I, primary and secondary amines can be substituted electrophilically. This constitutes a useful method of "umpolung" of usual amine reactivity, characterized by α -carbocationic nucleophilic substitution, as in the Mannich reaction.

Scheme I



One of the most widely studied classes of α -aza carbanions is that derived from nitrosamines.¹ The base catalyzed deuteration of dimethyl nitrosamine was first reported in 1966 by Rademacher and Lüttke.^{2,3} Later reports revealed that base catalyzed electrophilic substitution of nitrosamines with alkyl halides,⁴⁻⁶ aldehydes and ketones,^{7,8} and alkyl cyanides^{9,10} also proceed in high yields. Nitrosamines have been used in the synthesis of hemlock alkaloids,¹¹ fire ant venom alkaloids,¹² and tetrazines.¹³ Stereochemical studies of nitrosamine carbanions¹⁴⁻¹⁸ have shown that axial proton removal syn to the nitroso group is highly favored, suggesting carbanion stabilization from a 6π electron 4-atom system ($\frac{2}{\sim}$).



Another functional group that provides activation for α -aza carbanion formation is the carbonyl. α -Amido carbanions have been proposed as intermediates in the conversion of N,N-dimethylbenzamides to N-phenacylbenzamides,^{19,20} the ring enlargement of 1-benzyl-2-azetidinones,²¹ and the cyclization of N-alkyl-2-benzoylaminobenzenophenones.²² Trappable α -amido carbanions have been reported for N-benzyl and N,N-dibenzylbenzamides.^{23,24} A more general class of secondary 2,4,6-triisopropylbenzamides have been shown to form trappable carbanions readily.²⁵ Imides,²⁶ thioamides,²⁷ vinylogous amides^{28,29} and formamides³⁰⁻³³ have also been shown to undergo metallation and subsequent electrophilic substitution.

A third class of α -aza carbanions, originally reported in 1968,³⁴ that has been widely studied is derived from isonitriles.^{35,36} α -Isocyano carbanions³⁷ have been used in the lengthening of primary amines,³⁸ ring homologation,^{39,40} the synthesis of oxazoles,⁴¹⁻⁴³ oxazines,⁴⁴ oxazolines,^{34,45} α -amino acids,⁴⁶⁻⁴⁸ and unsymmetrical ketones.⁴⁹ α -Metallated alkenyl isocyanides⁵⁰ and aldimines^{48,51,52} also have been reported. Stereochemical studies of isocyano cyclopropanes show that substitution occurs with retention of configuration, suggesting dipole stabilization of the carbanion.^{53,54} Two other classes of α -aza carbanions which are considered to be dipole stabilized are polyazaindenes^{55,56} and pyridine N-oxides.⁵⁷⁻⁶⁰ The latter class has been found to undergo both electrophilic alkylation⁶¹ and acylation.⁶²

Two other groups of synthetically useful α -aza carbanions which have recently received a great amount of attention are 1,2-diazaallyllithium⁶³⁻⁶ and 2-azaallyllithium^{67,68} compounds. Each of these classes readily undergoes electrophilic substitution with aldehydes and ketones.

BIBLIOGRAPHY

1. D. Seebach and D. Enders, *Angew. Chem., Int. Ed.*, **14**, 15 (1975).
2. P. Rademacher, Ph.D. Thesis, University of Göttingen, 1966.
3. P. Rademacher and W. Lüttke, *Spectrochimica Acta*, **27A**, 715 (1971).
4. L. Keefer and C. Fodor, *J. Am. Chem. Soc.*, **92**, 5747 (1970).
5. D. Seebach, D. Enders, and B. Renger, *Ber.*, **110**, 1852 (1977).
6. D. Seebach and D. Enders, *Angew. Chem., Int. Ed.*, **11**, 301 (1972).
7. D. Seebach and D. Enders, *Ber.*, **108**, 1293 (1975).
8. D. Seebach and D. Enders, *Angew. Chem., Int. Ed.*, **11**, 1101 (1972).
9. D. Seebach and D. Enders, *Angew. Chem., Int. Ed.*, **11**, 1102 (1972).
10. D. Seebach, D. Enders, R. Dach, and R. Pieter, *Ber.*, **110**, 1879 (1977).
11. D. Enders, T. Hassel, R. Pieter, B. Renger, and D. Seebach, *Syn.*, 548 (1976).
12. R. Fraser and S. Passannanti, *Syn.*, 540 (1976).
13. D. Seebach, D. Enders, B. Renger, and W. Brügel, *Angew. Chem., Int. Ed.*, **12**, 495 (1973).
14. B. Renger, H. Kalinowski, and D. Seebach, *Ber.*, **110**, 1866 (1977).
15. D. Barton, R. Bracho, A. Gunatilaka, and D. Widdowson, *J. Chem. Soc. Perkin Trans.*, **1**, 579 (1975).
16. R. Lyle, J. Saavedra, G. Lyle, H. Fribush, and J. Marshall, *Tetrahedron Lett.*, 4431 (1976).
17. R. Fraser, T. Grindley, and S. Passannanti, *Can. J. Chem.*, **53**, 2473 (1975).
18. R. Fraser and L. Ng, *J. Am. Chem. Soc.*, **98**, 5895 (1976).
19. P. Beak and R. Farney, *J. Am. Chem. Soc.*, **95**, 4771 (1973).
20. P. Beak, G. Brubaker, and R. Farney, *J. Am. Chem. Soc.*, **98**, 3621 (1976).
21. T. Durst, R. Van Der Elzen and M. LeBelle, *J. Am. Chem. Soc.*, **94**, 9261 (1972).
22. H. Greuter and H. Schmid, *Helv. Chim. Acta*, **57**, 281 (1974).
23. A. Tischler and M. Tischler, *Tetrahedron Lett.*, 3 (1978).
24. R. Fraser, G. Boussard, I. Postescu, J. Whiting, and Y. Wigfield, *Can. J. Chem.*, **51**, 1109 (1973).
25. P. Beak, B. McKinnie, and D. Reitz, *Tetrahedron Lett.*, **22**, 1839 (1977).
26. R. Schlecher and D. Seebach, *Helv. Chim. Acta*, **60**, 1459 (1977).
27. D. Seebach and W. Lubosch, *Angew. Chem., Int. Ed.*, **15**, 313 (1976).

28. R. Schmidt and J. Talbiersky, *Angew. Chem., Int. Ed.*, 15, 171 (1976).
29. R. Schmidt and G. Berger, *Ber.*, 109, 2936 (1976).
30. R. Fraser and P. Hubert, *Can. J. Chem.*, 52, 185 (1975).
31. U. Schöllkopf and H. Beckhaus, *Angew. Chem., Int. Ed.*, 15, 293 (1976).
32. K. Smith and K. Swaminathan, *Chem. Commun.*, 307 (1976).
33. D. Seebach and W. Lubosh, *Ber.*, 109, 1309 (1976).
34. F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 6231 (1968).
35. D. Hoppe, *Angew. Chem., Int. Ed.*, 13, 789 (1974).
36. U. Schöllkopf, *Angew. Chem., Int. Ed.*, 16, 339 (1977).
37. W. Boll, F. Gerhart, A. Nürrenbach, and U. Schöllkopf, *Angew. Chem., Int. Ed.*, 9, 458 (1977).
38. U. Schöllkopf, K. Henneke, K. Madawinata, and R. Harms, *Ann.*, 40 (1977).
39. U. Schöllkopf and P. Böhme, *Angew. Chem., Int. Ed.*, 10, 491 (1971).
40. G. Niznik and H. Walborsky, *J. Org. Chem.*, 39, 608 (1974).
41. U. Schöllkopf and R. Schröder, *Angew. Chem., Int. Ed.*, 10, 333 (1971).
42. R. Schröder, U. Schöllkopf, E. Blume, and I. Hoppe, *Ann.*, 533 (1975).
43. A. Kozikowski and N. Hasan, *J. Org. Chem.*, 42, 2039 (1977).
44. U. Schöllkopf and R. Jentsch, *Angew. Chem., Int. Ed.*, 12, 323 (1973).
45. U. Schöllkopf, F. Gerhart, I. Hoppe, R. Harms, K. Hantke, K. Scheunemann, E. Eilers, and E. Blume, *Ann.*, 183 (1976).
46. K. Matsumoto, M. Suzuki, and M. Myoshi, *J. Org. Chem.*, 38, 2094 (1973).
47. U. Schöllkopf and R. Myer, *Ann.*, 1174 (1977).
48. N. Hirovatori and H. Walborsky, *J. Org. Chem.*, 39, 604 (1974).
49. O. Possel and A. van Leusen, *Tetrahedron Lett.*, 4229 (1977).
50. U. Schöllkopf, D. Stafforst, and R. Jentsch, *Ann.*, 1167 (1977).
51. G. Nizik, W. Morrison III, and H. Walborsky, *J. Org. Chem.*, 39, 600 (1974).
52. M. Periasamy and H. Walborsky, *J. Org. Chem.*, 39, 611 (1974).
53. H. Walborsky and M. Periasamy, *J. Am. Chem. Soc.*, 96, 3711 (1974).
54. M. Periasamy and H. Walborsky, *J. Am. Chem. Soc.*, 99, 2631 (1977).
55. W. Paudler and H. Shin, *J. Org. Chem.*, 33, 1087 (1968).
56. W. Paudler and L. Helmick, *J. Org. Chem.*, 33, 1087 (1968).
57. J. Zoltewicz and G. Kauffmann, *Tetrahedron Lett.*, 337 (1967).
58. W. Paudler and S. Humphrey, *J. Org. Chem.*, 35, 3469 (1970).
59. J. Zoltewicz and L. Helmick, *J. Am. Chem. Soc.*, 92, 7547 (1970).
60. S. Krueger and W. Paudler, *J. Org. Chem.*, 37, 4188 (1972).
61. R. Abramovitch, E. Smith, E. Knaus, and M. Saka, *J. Org. Chem.*, 37, 1690 (1972).
62. R. Abramovitch, R. Coutts, and E. Smith, *J. Org. Chem.*, 37, 3584 (1972).
63. R. Beutler, B. Zeek, and E. Müller, *Ber.*, 102, 2636 (1969).
64. E. Wenkert and C. McPherson, *J. Am. Chem. Soc.*, 94, 8084 (1972).
65. U. Schöllkopf, B. Bánhidai, H. Frasnelli, R. Meyer, and H. Beckhaus, *Ann.*, 1767 (1974).
66. T. Kauffmann, D. Berger, B. Scheerer, and A. Woltermann, *Ber.*, 110, 3034 (1977).
67. T. Kauffmann, H. Berg, E. Köppelmann, and D. Kuhlmann, *Ber.*, 110, 2659 (1977).
68. T. Kauffmann, U. Koch, F. Steinseifer, and A. Vahrenhorst, *Tetrahedron Lett.*, 341 (1977).

AROMATIC EXCIMERS

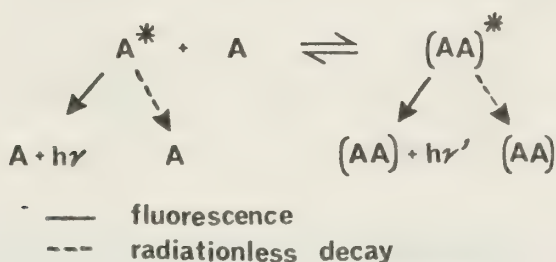
Reported by M. J. Darmon

March 9, 1978

Ever since 1954, when Förster and Kasper¹ reported the detection of weak red-shifted structureless fluorescence from a concentrated solution of pyrene without a corresponding feature in the absorption spectrum, the field of excimers as distinct photochemical entities has rapidly expanded.²

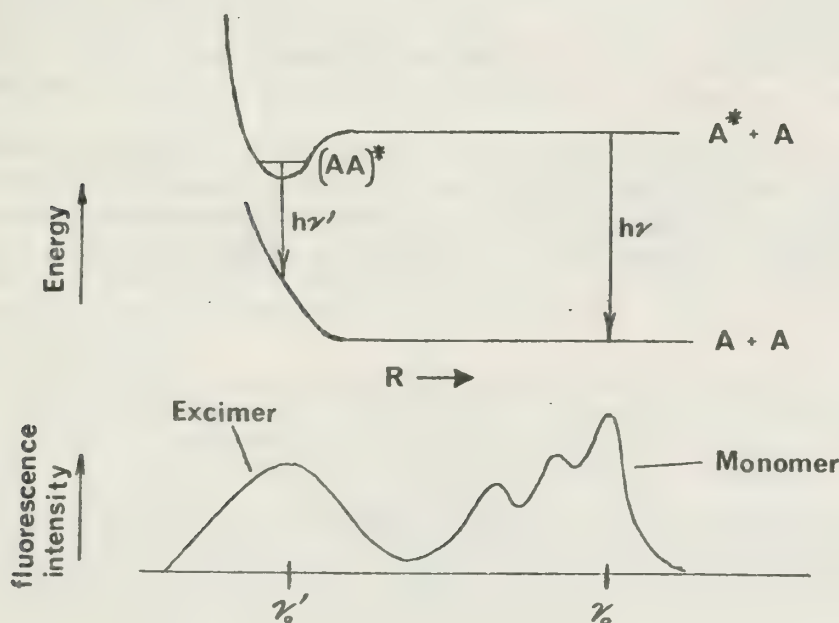
The word excimer is a hybrid of the phrase: excited-state-dimer.³ Birks defines it as a molecular dimer or stoichiometric complex which is associated in an excited electronic state and which is dissociative in its ground electronic state.⁴ The simplest process involved in the interaction of an excited state molecule with a ground state component to form an excimer is represented in Scheme I.⁵ All of the components can undergo the typical photochemical reactions expected of excited state molecules.

Scheme I



Stevens and Ban⁶ proposed a parallel sandwich configuration as the most plausible for the approach of two aromatic components. A potential energy diagram illustrates the energetics of excimer formation (Figure 1).

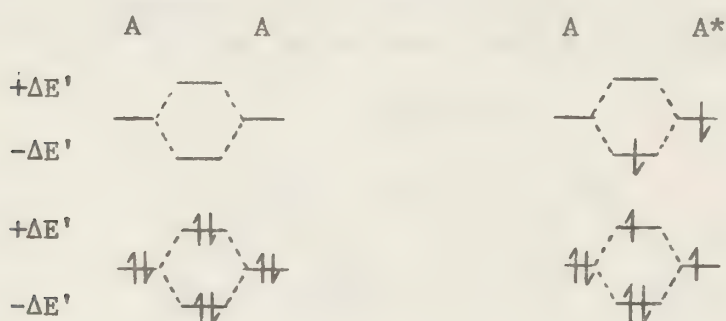
Figure 1



In the ground state the repulsive energy increases at decreasing inter-nuclear distances between the two planes. By contrast, in the excited state an energy stabilization occurs at a distance where repulsive forces should have come into effect. The stabilization as calculated from a spectral shift is smaller than expected due to the necessary inclusion of the ground state repulsive energy. The stabilization energy can be as high as 10 kcal/mol for the pyrene system.

A simple M.O. diagram best illustrates why excimers exist (Figure 2). In the ground state the molecules would achieve zero stabilization upon binding. However, when one of the components is photochemically excited, a net stabilization of $\Delta E + \Delta E'$ is achieved in the bound excimer state.

Figure 2



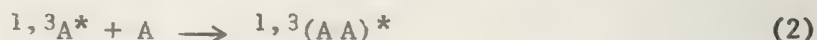
The following wave function is proposed to explain the stability of an excimer (Eq. 1).⁷ The exciton resonance integral is the result of a

$$\Psi = c_1[\Psi(A^*A) + \Psi(AA^*)] + c_2[\Psi(A^+A^-) + \Psi(A^-A^+)] \quad (1)$$

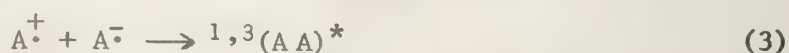
exciton resonance charge transfer

delocalization of the excitation between both aromatic molecules.⁸ The charge transfer integral is attributed to a charge resonance in the excited encounter complex.⁹ The c_1/c_2 ratio may vary with each individual excimer system, but quantum chemical calculations show both exciton and charge resonance are necessary to explain the formation of an excimer.¹⁰

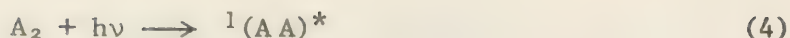
Excimer formation can be attributed to many mechanisms. The most common method, as previously mentioned, is the formation of the complex by a ground state molecule combining with another molecule in an excited singlet or triplet state (Eq. 2). Electron transfer from a radical anion



to a radical cation is also responsible for excimer production (Eq. 3).¹¹

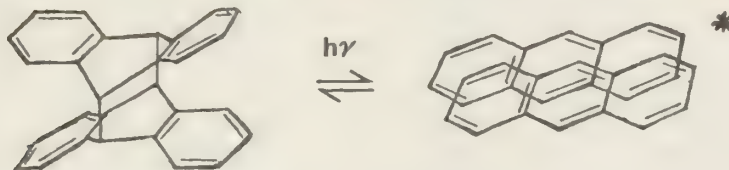


Recently, Brocklehurst and co-workers have used the method indicated by Eq. 3 to observe the excimer fluorescence of trans-stilbene and diphenylacetylene in squalene at 77°K by gamma radiation.¹² Photolysis of a photodimer in a rigid glass matrix produces molecules in a sandwich configuration which can emit excimer fluorescence (Eq. 4). Anthracene and its derivatives are known to undergo dimerization at the 9,10 positions.

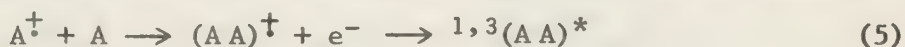


Such dimers trapped in a rigid glass matrix,¹³ in solution, and in crystals¹⁴ have been used to produce the corresponding excimers (Scheme II).

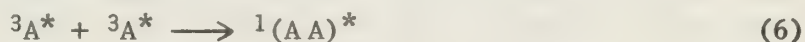
Scheme II



When liquid alkylbenzenes are excited by an intense beam of electrons an excimer fluorescence is observed. The observation is attributed to the mechanism of dimer cation neutralization (Eq. 5).¹⁵ The last mechanism



proposed is that of triplet-triplet annihilation of two molecules forming an excimer in the singlet excited state (Eq. 6).¹⁶



As discussed by Birks,⁴ the ability of aromatic molecules to form excimers and/or photodimers depends on which category they belong to. Based on an examination of the attractive potential, $E(r)$, and the repulsive potential, $R(r)$, the three categories are as follows:

- A. $E(r) \gg R(r)$: production of photodimers and excimers, e.g., anthracene and tetracene.
- B. $E(r) > R(r)$: production of excimers, e.g., benzene, naphthalene, pyrene, 1,2-benzanthracene, 3,4-benzphenanthrene, and triphenylene.
- C. $E(r) < R(r)$: no excimer production, e.g., phenanthrene and and chrysene.

The involvement of these electronic interactions can be seen in the dimerization of the 9-substituted anthracenes. Dimerization of 9-cyclohexylantracene proceeds quite readily, whereas 9-phenyl anthracene must be irradiated with a perylene sensitizer to bring about dimerization.¹⁷ The fact that a relatively crowded cyclohexyl substituent allows dimerization to proceed more easily tends to support the involvement of an electronic interaction.

The original work done by Förster and Kasper on the pyrene system best illustrates the production of and factors influencing excimers. As seen in Figure 3, the fluorescence spectrum of pyrene monomer is a well defined, structured emission. But, as the concentration of pyrene in a solution of n-heptane at 20°C is increased, the monomer fluorescence decreases and the structureless, red-shifted excimer fluorescence increases. The isoemissive point is attributed to the fluorescence of only two components in this spectrum. An examination of the concentration dependence of fluorescence intensity indicates a bimolecular reaction mechanism as shown in Eq. 2 (Figure 4).^{2b}

Figure 3

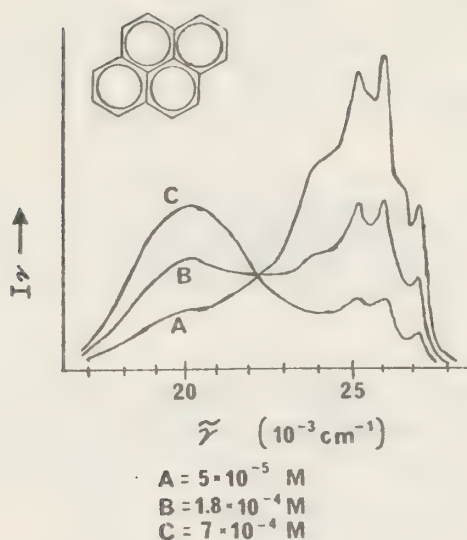
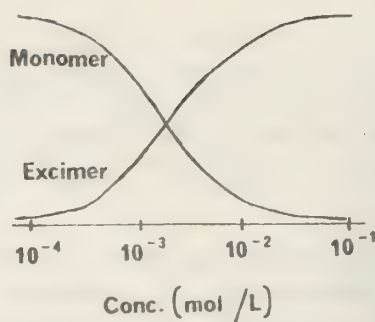


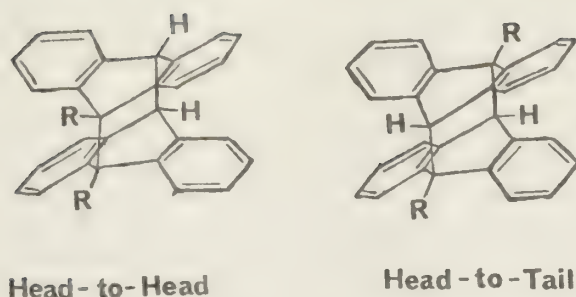
Figure 4



The rate of excimer formation has been determined to be diffusion controlled in many of the aromatic systems studied to date. Therefore, the rate of excimer production depends on the viscosity of the solvent.^{2b} Since the viscosity of a solvent is usually temperature dependent, the rate of excimer formation is also temperature dependent. However, a number of other factors are influenced by temperature effects. The lifetime of the excimer is determined by its relative stability. Some aromatic excimers are less tightly bound; for example, benzene and anthracene have dissociation enthalpies of 5-6 kcal/mol.¹⁸ Nevertheless, just like pyrene with a dissociation enthalpy of 10-11 kcal/mol,¹⁹ they possess a dissociation entropy of about 20 cal/deg·mole. Depending on the aromatic system investigated, a set of opposing forces operates. At low temperatures, the excimer predominates, but as temperature increases, molecular dissociation causes the excimer to separate into the monomeric components.²⁰ A pressure dependence has also been noted for excimer formation, for as the pressure is increased (1 to 5 kbar for 1,6-dimethylnaphthalene in *n*-heptane), excimer fluorescence also increases. Calculations from volume contraction experiments result in an interplanar distance of approximately 3.0 Å in the excimer.²¹

Another important factor involved in the ability to produce excimers is steric interaction. Substituents on an aromatic component influence whether π -overlap can occur before steric repulsion becomes a critical factor. A good example is the case of the 9-substituted anthracenes. Many dimerize, but only in the head-to-tail, as opposed to the head-to-head, configuration (Figure 5).²² Intramolecular excimer formation presents the most interesting aspect of a steric manipulation of a biochromophoric molecule held together by a definite length of "flexible molecular chain". Since these excimers are formed intramolecularly, they are completely concentration independent, so other factors can be more easily studied. Original work by Hirayama on diphenyl alkanes demonstrated that the alkane chain had to be three carbons in length to observe excimer emission.²³ For a long time afterward this $n=3$ rule prevailed.²⁴ It was felt that long chains would result in monomer emission because of the entropy effect of a higher number of competitive conformations. However, the so-called $n=3$ rule has since been broken by a

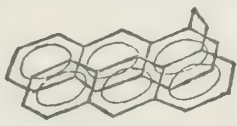
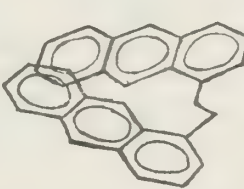
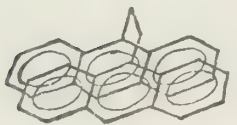
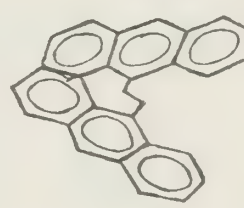
Figure 5



number of new intramolecular systems. Birks has shown excimer emission of 1,4-bisnaphthylbutane.²⁵ De Schryver's work on N,N'-alkylenebismaleimides has expanded the chain length to $n=6$ and he has been able to push it up to $n=11$ for biscoumarins.²⁶

Temperature studies on 1,2-dianthrylethanes have proven that more than one excimer can be formed for a particular molecular system. Table 1 shows that at 77°K maximum overlap is preferred but a weaker excimer, as shown by an excimer emission at a shorter wavelength indicating a smaller π overlap and electronic interaction, is found at 300°K.²⁷

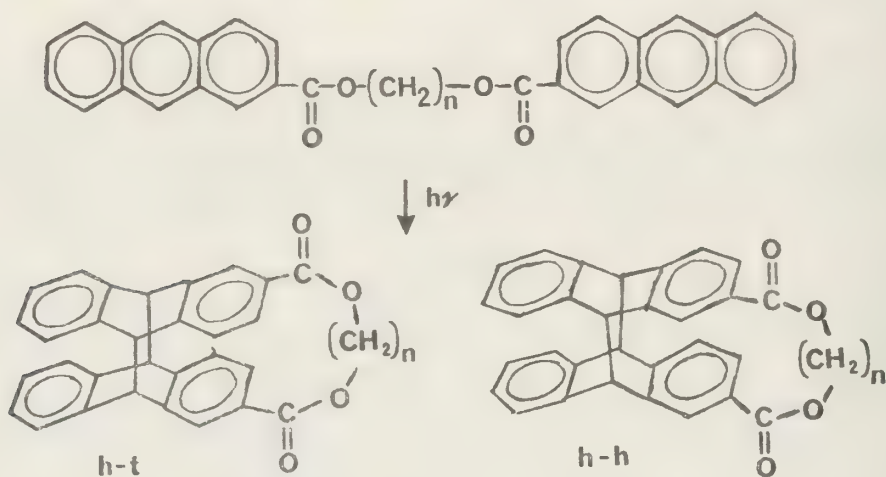
Table 1

$\lambda_m(\text{nm})$	77°K	300°K	$\lambda_m(\text{nm})$
530			460
530			460

In the paracyclophanes, in which the aromatic units are more rigidly secured to one another, excimer emission has also been studied. Only excimer fluorescence is found for [4,4]-paracyclophane while none is found for the [4,5] and [6,6] homologs. The difference in behavior is explained by steric inhibition preventing contraction of the two planar aromatic units in the latter two systems.^{2b} In [4,4]-paracyclophane, the two benzene rings are separated by 3.73 Å (x-ray) and are found to contract to 3.3 Å to form the excimer.²⁸ The [2,2]-paracyclonaphthanes [2,2]-paracycloanthracenes, which have distorted aromatic rings, similarly result in excimer production and finally in photodimerization.⁴

Whether excimers are the photochemical intermediates involved before dimerization of aromatic components occurs has been an elusive question. Only a short description of the evidence favoring this mechanism will be given. Qualitatively, the photoreversible cyclomerization of 1,3 bis(α -naphthyl)propane which is accompanied by excimer fluorescence is supportive of this mechanism.²⁹ The same argument can be used for anthracene and its derivatives. Photodimerization and excimer emission are usually in direct competition and this can be seen when bulky substituents are placed on the 9 or 10 position.¹⁶ Recent energy transfer experiments point to the excimer as an intermediate.³⁰ Very recent experimentation by De Schryver on a series of bis-2-anthroates showed a very interesting result. Upon irradiation, two cyclomers were produced. The ratio of head-to-head vs. head-to-tail cyclomers was attributed to the operation

Scheme III



n	%(h-t)	%(h-h)	ϕ cyclomerization
2	10	90	0.07
3	20	80	0.09
4	30	70	0.08
5	35	65	0.11
7	40	60	0.06
9	52	48	0.05

of two mechanisms and was a function of chain lengths. It is believed that the head-to-head was produced by an excited singlet state and the head-to-tail isomer was produced via an excimer intermediate.³¹

Whether excimers are intermediates in photodimerization or merely passive bystanders, the fact is that they are photochemical entities which have a unique existence. They have even been postulated as a protective mechanism for DNA against UV radiation damage.³² Study of excimer systems has revealed much about the energetics and photophysics of molecular systems, and they still hold much more information about the deceptively simple photochemical process.

BIBLIOGRAPHY

1. Th. Förster and K. Kasper, *Z. Phys. Chem.*, N. F. 1, 275 (1954).
2. (a) M. Gordon and W. R. Ware, ed., "The Exciplex", Academic Press, New York, 1975; (b) Th. Förster, *Angew. Chem. Int. Ed.*, 8, 333 (1969).
3. B. Stevens and E. Hutton, *Nature (London)*, 186, 1045 (1960).
4. J. B. Birks, "The Exciplex", M. Gordon and W. R. Ware, ed., Academic Press, New York, 1975, p. 39.
5. E. Döller and Th. Förster, *Z. Phys. Chem.*, N. F. 34, 132 (1962).
6. B. Stevens and M. I. Ban, *Trans. Faraday Soc.*, 60, 1515 (1964).
7. Th. Förster, "The Exciplex", M. Gordon and W. R. Ware, ed., Academic Press, New York, 1975, p. 1.
8. Th. Förster and K. Kasper, *Z. Elektrochem.*, 59, 976 (1955).
9. J. Ferguson, *J. Chem. Phys.*, 28, 765 (1958).
10. (a) J. N. Murrell and J. Tanaka, *Molecular Physics*, 7, 363 (1964); (b) A. Warshel and Z. Shakked, *J. Am. Chem. Soc.*, 97, 5679 (1975).
11. E. A. Chandross, J. W. Longworth and R. E. Visco, *J. Am. Chem. Soc.*, 87, 3259 (1965).
12. B. Brocklehurst, D. C. Bull, M. Evans, P. M. Scott, and G. Stanney, *J. Am. Chem. Soc.*, 97, 2977 (1975).
13. E. A. Chandross and J. Ferguson, *J. Chem. Phys.*, 45, 397 (1966).
14. J. Ferguson and A. W.-H. Mau, *Mol. Phys.*, 27, 377 (1974).
15. J. B. Birks, *Chem. Phys. Letters*, 4, 603 (1970).
16. J. B. Birks, "Photophysics of Aromatic Molecules", Wiley-Interscience, New York, 1970.
17. (a) R. D. Campbell and R. S. S. Liu, *Mol. Photochem.*, 6, 207 (1974); (b) R. D. Campbell and R. S. S. Liu, *Chem. Commun.*, 1191 (1970).
18. (a) J. B. Birks, C. L. Braga, and M. D. Lumb, *Proc. Roy. Soc. (London)*, A 283, 83 (1965); (b) J. B. Aladekomo and J. B. Birks, *Proc. Roy. Soc. (London)*, A 284, 551 (1965).
19. E. Döller and Th. Förster, *Z. Physik. Chem.*, N. F. 34, 132 (1962).
20. E. Döller and Th. Förster, *Z. Physik. Chem.*, N. F. 31, 274 (1962).
21. H. Braum and Th. Förster, *Ber. Bunsenges. Physik. Chem.*, 70, 1092 (1966).
22. D. O. Cowan, R. L. Drisco, "Elements of Organic Photochemistry", Plenum Press, New York, 1976.
23. F. Hirayama, *J. Chem. Phys.*, 42, 3163 (1965).
24. W. Klöpffer, *Chem. Phys. Letters*, 4, 193 (1969).
25. E. A. Chandross and C. J. Dempster, *J. Am. Chem. Soc.*, 92, 3586 (1970).
26. J. Put and F. C. De Schryver, *J. Am. Chem. Soc.*, 95, 137 (1973).
27. T. Hayashi, N. Mataga, Y. Sakata, S. Misumi, M. Morita, and J. Tanaka, *J. Am. Chem. Soc.*, 98, 5910 (1976).
28. W. Klöpffer, "Organic Molecular Photophysics", J. B. Birks, ed., Vol. 1, Wiley-Interscience, New York, 1973, p. 357.
29. E. A. Chandross and C. J. Dempster, *J. Am. Chem. Soc.*, 92, 703, 3586 (1970).
30. M. D. Cohen, A. Ludmer, and V. Yakhot, *Chem. Phys. Letters*, 38, 398 (1976).
31. N. Boens, M. DeBrackeleire, J. Huybrechts, and F. C. De Schryver, *Z. Phys. Chem.*, N. F. 101, 27 (1976).
32. (a) J. Eisinger, *Photochem. Photobiol.*, 7, 597 (1968); (b) A. A. Lamola and J. Eisinger, *Proc. Nat. Acad. Sci. U.S.*, 59, 4 (1968).

THE SYNTHESIS AND REACTIONS OF AMINIMIDES

Reported by Michael R. Ross

March 13, 1978

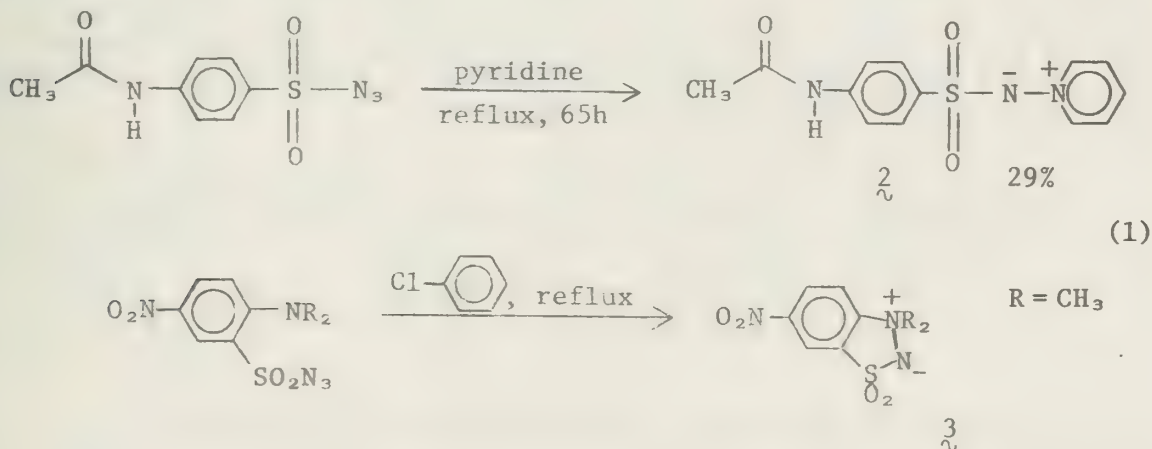
Aminimides, dipolar ions containing a cationic nitrogen bonded to an anionic nitrogen, were first prepared by Curtius in 1930¹ in a reaction of sulfonyl azides with pyridine. It was subsequently established that aminimides could also be synthesized from acyl azides, acyl and sulfonyl hydrazides, alkyl azidoformates, 1-aminopyridinium halides, and 1,1,1-trimethylhydrazinium salts.² Aminimides have found widespread use in industry as adhesives, detergents, antistatic agents, surface coatings, elastomers, and in other applications.²

The nomenclature employed in describing aminimides is varied. However, the most useful, that of Chemical Abstracts, names aminimides as the inner salts of hydrazinium ions. For example, aminimide 1 is 1,1,1-trimethyl-2-benzoylhydrazinium hydroxide, inner salt. The non-systematic name for 1 is trimethylamine-benzimide.



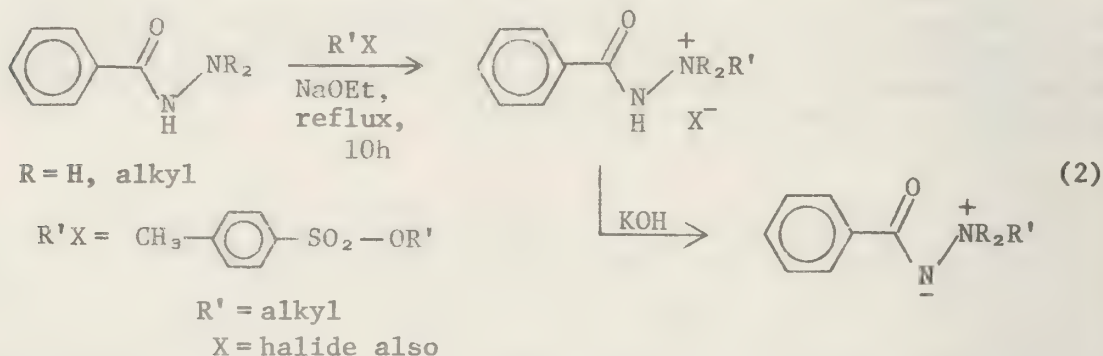
The most intensively studied aminimides, the amine acylimides, show absorption in the infrared in the 1550-1590 cm^{-1} region. This is supportive of resonance of the type shown in 1. This resonance is reflected in the basicity of aminimides and in acylation and alkylation reactions, to be discussed subsequently.

Synthesis of Aminimides. Sulfonyl azides react with substituted pyridines to form pyridine-1-sulfonylimides such as 2³ (Eq. 1) and other products, a reaction first demonstrated by Curtius and his co-workers.⁴ However, it was found that the reaction of arenesulfonyl azides with saturated tertiary amines did not produce aminimides:⁵ p-toluenesulfonyl azide with tributylamine and triethylamine gave p-toluenesulfonamide (46% isolated yield), whereas dimethylaniline reacted with benzene-sulfonyl azide to give p-dimethylaminobenzenesulfonanilide (22% yield). Sulfonyl azides having ortho-substituted dialkylamino groups may form cyclic aminimides such as 3.⁶



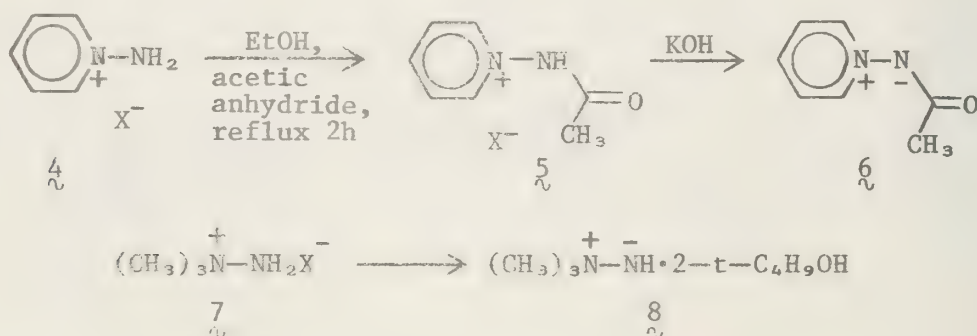
Aminimides may also be prepared by the reaction of alkyl azidoformates with pyridines and cyanoazide with trialkylamines.⁷ It has been proposed that the products formed in the reactions of sulfonyl and acyl azides with the amines may be rationalized as being due to the formation of an intermediate singlet nitrene.⁸ Again, as with the sulfonyl azides, attempts to extend the alkyl azidoformate reaction to trialkylamines failed. Thus, thermolysis of 2-dialkylamino-5-nitrobenzoyl azides yielded only the isocyanate; however, cyanoazide did react with trisubstituted amines to give the aminimides.⁹

Aminimides have also been synthesized from the corresponding sulfonyl¹⁰ and acylhydrazides¹¹ in a sequence involving alkylation of the hydrazide followed by treatment with strong base, as in Eq. 2. The

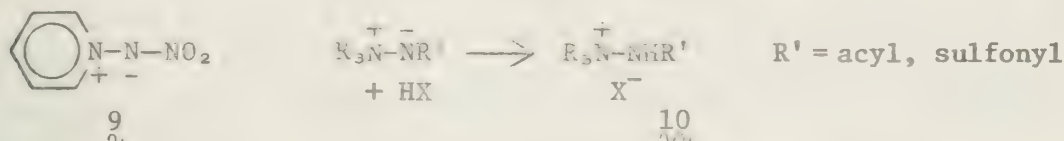


dialkylhydrazides have been prepared by the action of an acid chloride on the 1,1-disubstituted hydrazine.¹² The alkylating agent in the first step in Eq. 2 (for the acyl hydrazides) may be either an alkyl halide or an alkyl p-toluenesulfonate, whereas for the sulfonylhydrazides, the alkylation step is not as general, having been successfully applied only with methyl iodide and benzyl bromide.¹³ This procedure has also worked well for hydrazides synthesized from substituted hydrazines and chloroformates, isocyanates, and chlorothioformates.¹⁴

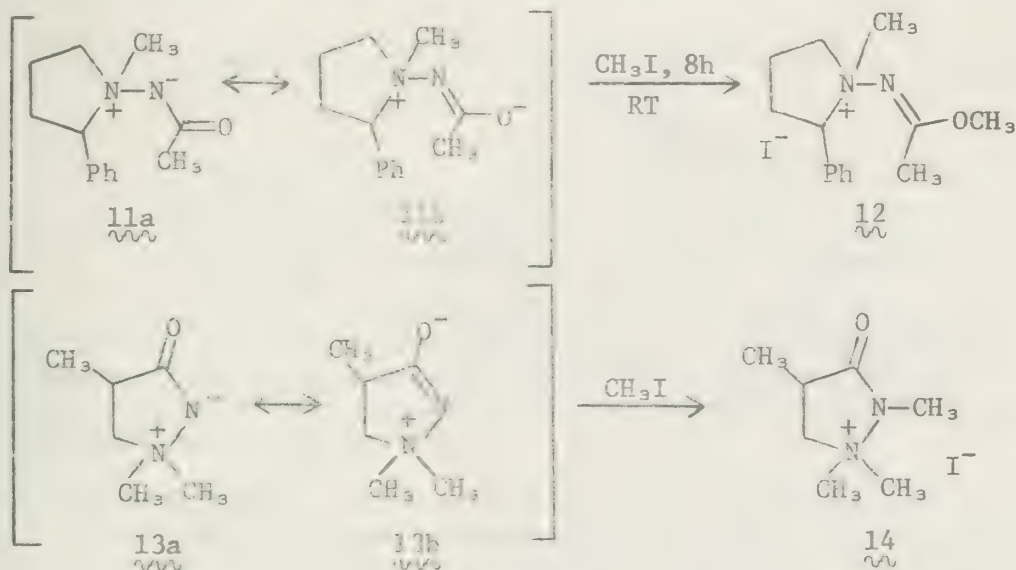
1-Aminopyridinium halides, prepared by causing pyridine to react with hydroxylamine-O-sulfonic acid and then with HI or HCl,¹⁵ form acylamino derivatives upon treatment with acetic anhydride. These are convertible to the aminimide with the addition of strong alkali.¹⁶ In a similar manner, aminimides may be synthesized from 1-alkyl-1,1-dimethylhydrazinium halides.¹⁷ Finally, 1,1,1-trimethylhydrazinium halides, when treated with a strong base, such as potassium t-butoxide in t-butanol, form aminimines such as **8** which are coordinated with two molecules of alcohol and are very strong bases, reacting with isocyanates, acid chlorides, and sulfonyl chlorides to form the corresponding aminimides.¹⁸



Reactions of Aminimides. Aminimides are mild bases with pKa's between 3.0 and 5.0; a notable exception is aminimide 9, with a pKa of -4.6.^{15a} As bases, aminimides react with both organic and inorganic acids at room temperature to yield the corresponding hydrazinium salts, such as 10, while more vigorous reaction conditions result in decomposition. For example, aminimide 9 is converted into 1-aminopyridinium chloride, acetic acid, and sulfamic acid upon treatment with HCl under reflux for two hours.^{15a} By contrast, aminimides are in general inert to alkali.¹⁹

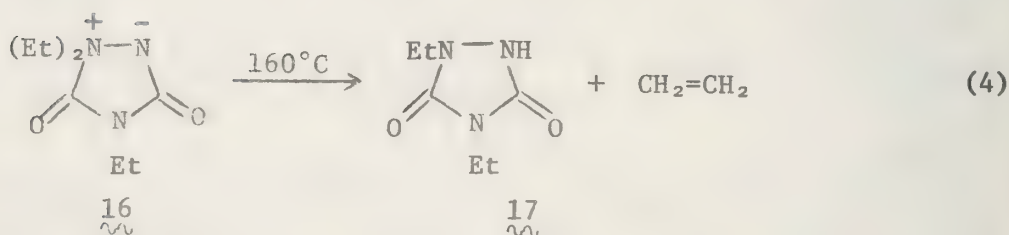
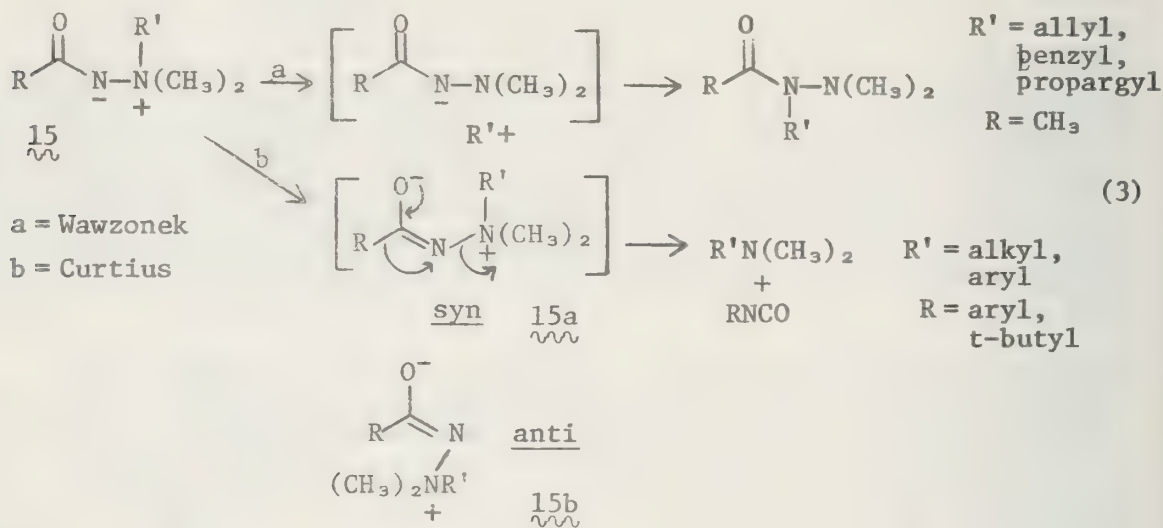


One can expect from the charge delocalization in acylaminimides as indicated in 1 that alkylation may occur at either oxygen or nitrogen. Upon treatment with methyl iodide, aminimide 11 gave O-alkylated product, 12,²⁰ while aminimide 13 formed the N-alkylated product, 14.²¹ In general, aminimides derived from pyridines or quinolines and 4- or 5-membered ring aminimides underwent alkylation at nitrogen, whereas aminimides in which the anionic nitrogen was not bonded to an aromatic ammonium nitrogen and was not part of a cyclic structure, were alkylated on oxygen. Nitrogen alkylation in cyclic aminimides may be a manifestation of ring strain: an S_N2 transition state involving N⁻ displacement of I⁻ from methyl iodide and resembling the ground-state contributor 13a will be less strained than that in which an endocyclic double bond is developing. N-alkylation would thus be favored. N-alkylation also occurs on aminimides derived from pyridines or quinolines, which have planar ammonium centers. The preferred alkylation on oxygen observed with such aminimides as 11 may be due to the greater steric accessibility of the oxygen compared with the nitrogen adjacent to a tetrahedral ammonium center. Presumably kinetically controlled rather than thermodynamically controlled product formation was being observed.

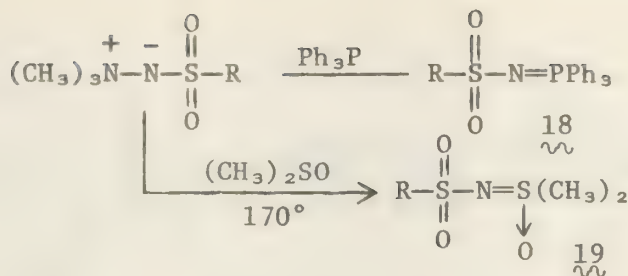


Acylaminimides, when thermally decomposed above their melting points, give products resulting from elimination, N-N bond cleavage, and rearrangement. The decomposition pathway is, of course, dependent on the structure

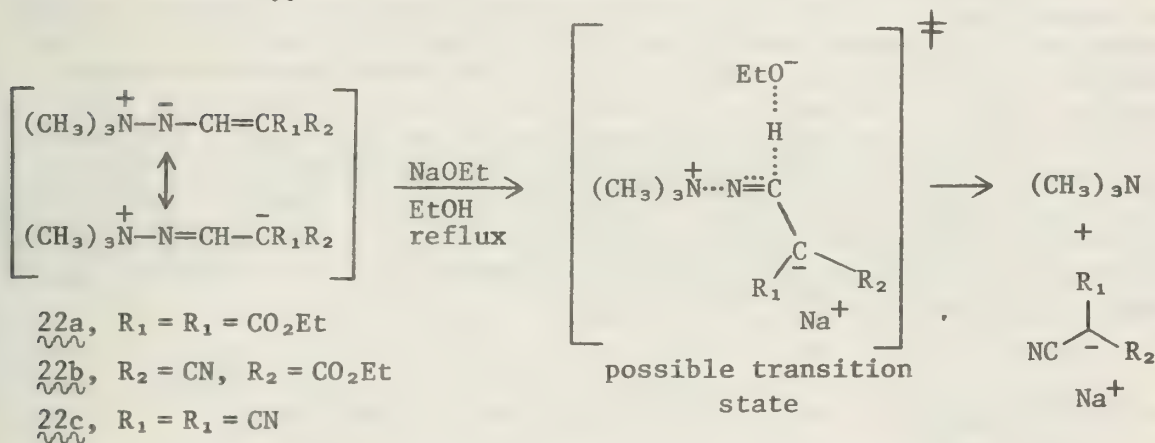
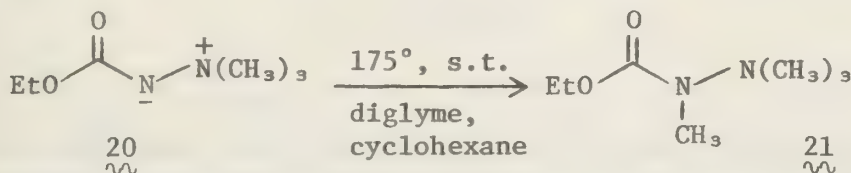
of the aminimide. Aminimides such as 15 give predominantly Curtius rearrangement product as the size of the R acyl group is increased. This is reflective of the isomeric structure 15a: the greater the steric bulk of R, the greater the proportion of syn isomer, and the greater the Curtius rearrangement product.^{22a} The Curtius pathway is also preferred when the cationic nitrogen is alkyl or aryl substituted and R is sterically bulky.^{22a} On the other hand, when the cationic nitrogen is substituted with an allyl, benzyl, or propargyl group, rearrangement proceeds via the "Wawzonek rearrangement", similar to the Stevens pathway of nitrogen ylids, with migration of the allyl (with inversion) or benzyl groups to the anionic nitrogen, if R is sterically small and the anti isomeric structure 15b is favored.^{23,24} It is not clear that the allyl, benzyl, and propargyl compounds proceed by the same mechanism. The allylic inversion argues for a cyclic intramolecular route in this case. The rearrangement of the benzyl group is also uncertain. The possibility of propargyl "inversion" was not investigated. The possibility of intermolecular migration was not checked by labeling studies, which would appear to be capable of easy design. Cyclic aminimides undergo the Wawzonek rearrangement almost exclusively, even if the cationic nitrogen is not allyl or benzyl substituted.²⁴ In a third decomposition pathway, those aminimides bearing a group with two or more carbons attached to N⁺ and a β-hydrogen cis-eliminate like amine-oxides upon thermolysis, as in the case of aminimide 16.²⁵



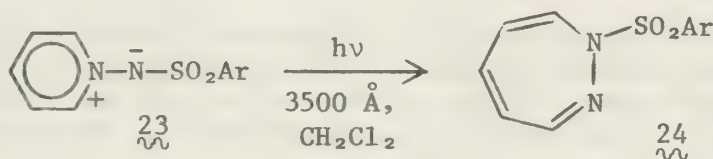
Sulfonyl aminimides give thermolysis products derived from nitrenes. The intermediacy of nitrenes was suggested by decomposition studies in the trapping agents triphenylphosphine and dimethyl sulfoxide, in which a triphenylphosphine sulfonimide such as 18 and a sulfoxime such as 19 were produced.²⁶



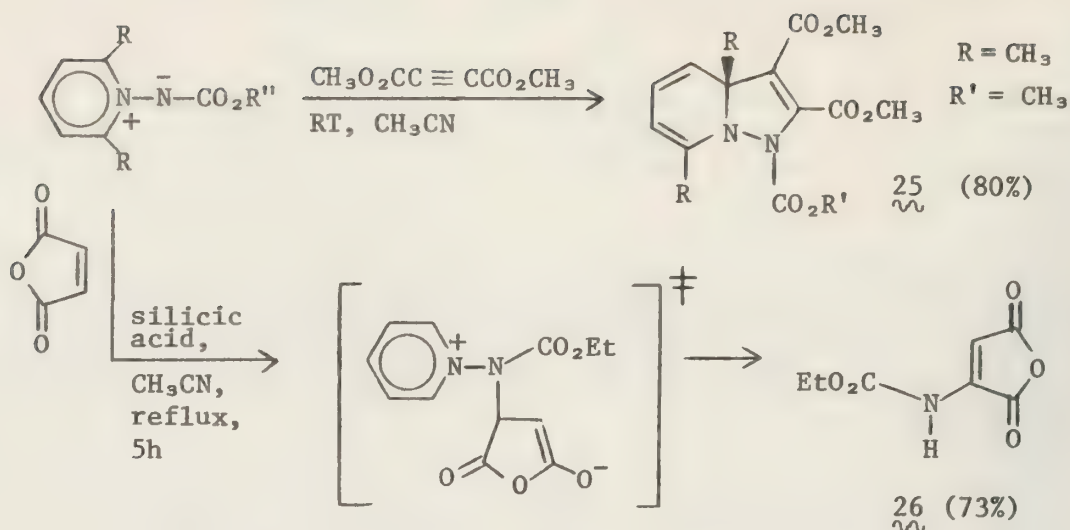
Carbethoxyaminimides such as 20 give exclusively Wawzonek rearrangement product on thermolysis, while some nitroaminimides are stable to 200°C for short periods.^{27b} It has also been reported that aminimides such as 22a-c undergo decomposition in the presence of sodium ethoxide - ethanol at reflux.²²



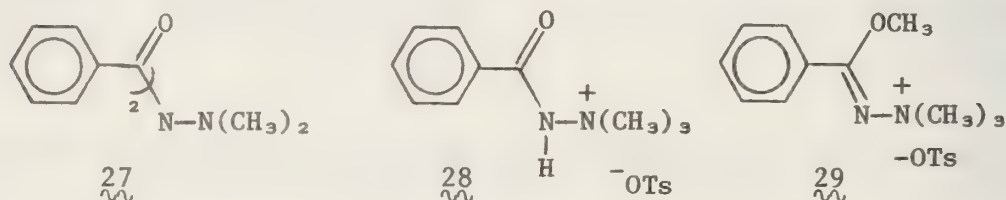
Aminimides such as 23 upon photolysis form diazepines such as 24.²⁸



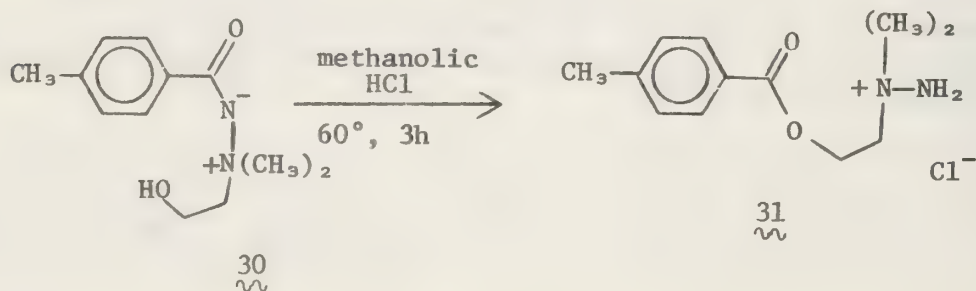
Aminimides derived from pyridine react with dimethyl acetylenedicarboxylate²⁹ in a 1,3 dipolar cycloaddition to form dihydropyrazolopyridines such as 25, and with α,β-unsaturated carbonyl compounds to form enamines such as 26.²⁹

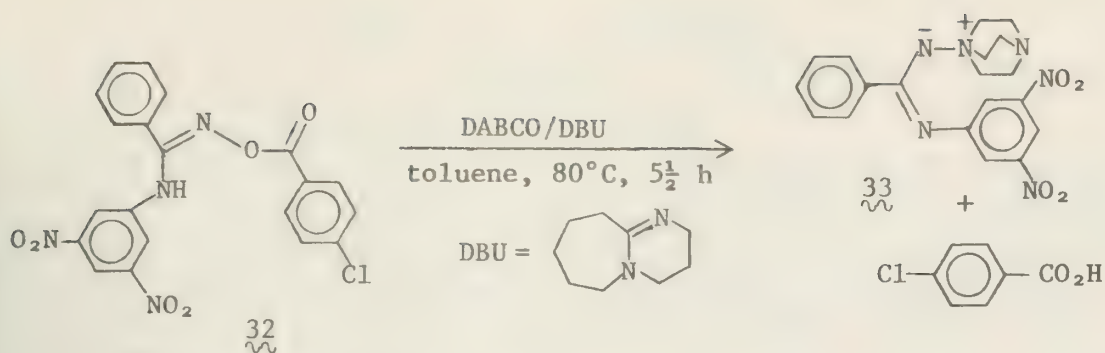


The diarylhydrazine 27 reacts with two equivalents of methyl p-toluenesulfonate at 120°C to afford a product mixture containing benzoic anhydride, p-toluenesulfonic acid, 1,1,1-trimethyl-2-benzoylhydrazinium tosylate (28), and 1,1,1-trimethyl-2- α -methoxybenzylidenehydrazinium tosylate (29).³⁰ Apparently, 27 reacts with an equivalent of methyl tosylate to form aminimide 1 and the mixed anhydride benzoyl p-toluenesulfonate, which disproportionates to benzoic anhydride and p-toluenesulfonic anhydride (confirmed in an independent experiment). Once formed, the sulfonic anhydride hydrolyzes to sulfonic acid. The aminimide then reacts with either another equivalent of methyl tosylate to afford 29 or with the sulfonic acid to produce 28.

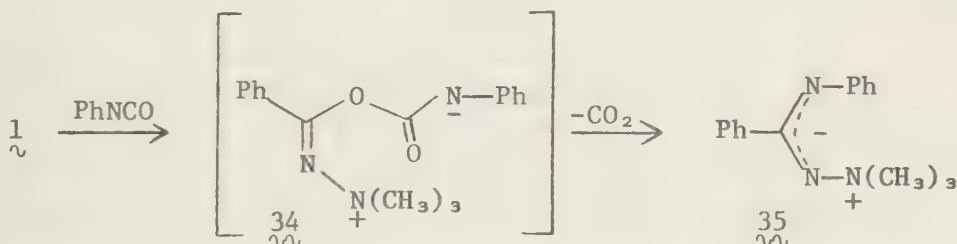


Upon treatment with aqueous HCl, aminimide 30 undergoes an intramolecular acyl rearrangement reaction to hydrazinium ester 31.³¹ Reaction of amidoxime ester 32 with DABCO in the presence of diaza-1,5-bicyclo[5.4.0]undec-5-ene (DBU) produces aminimide 33 and p-chlorobenzoic acid.³²

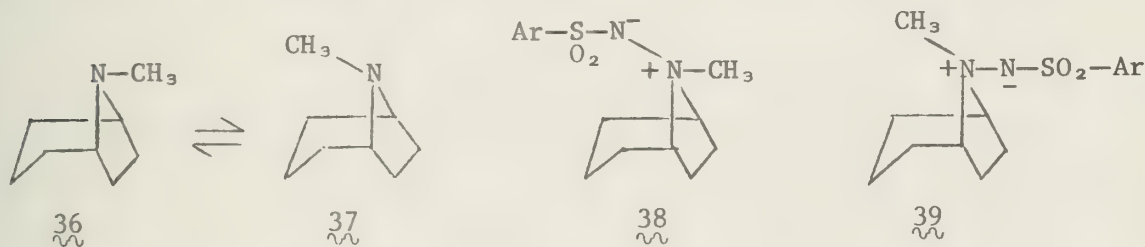




Aminimides such as **1** react with isocyanates to form intermediate ylids such as **34**, which decompose at room temperature to form amidrazones such as **35**.³³



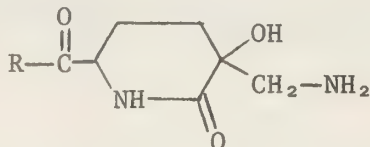
The position of the N-methyl equilibrium in N-methyltropenes (**36** \rightleftharpoons **37**) has been investigated by a product study in which an equilibrium system of **36** and **37** at 27°C was subjected to p-toluenesulfonyl azide under photolytic conditions. The nitrene produced reacted unselectively kinetically with the amines and afforded a mixture of diastereomeric aminimides, **38** and **39**, from which it was possible to deduce the position of the amine equilibrium and the free energy involved ($-\Delta G^{\circ}_{300} = 0.86$ kcal/mole in $\text{CCl}_2\text{FCClF}_2$, with aminimides **38** and **39** in a 4.2:1 ratio as isolated).³⁴ The nitrene has been shown^{35a} in competition experiments not



to discriminate between diisopropyl sulfide and dimethyl sulfide in the reaction to produce iminosulfuranes $p\text{-MeC}_6\text{H}_4\text{SO}_2\text{N}=\text{SR}_2$, and it has been shown that a similar lack of selectivity occurs in a reaction of the nitrene with butyl- and isobutyldimethylamines in the competitive conversion of the amines into aminimides $p\text{-MeC}_6\text{H}_4\text{SO}_2\text{N}=\text{NMe}_2\text{R}$, with a rate constant ratio of 1.0:1.0.³⁴ It has also been shown that the nitrene adds equally to each nitrogen of 1,2,4-trimethylpiperazine.^{35b} Thus, it was expected that the nitrene would be kinetically unselective between the N-methyltropene conformers, with photolysis and nitrene attack occurring much faster than equilibrium between the conformers.

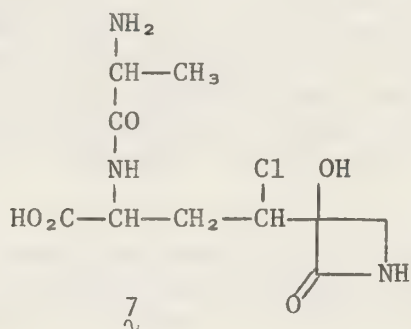
24. (a) W. S. Wadsworth, Jr., *J. Org. Chem.*, 31, 1704 (1966); (b) D. G. Morris, *Ind. Chim. Belge*, 36, 1060 (1971).
25. (a) W. Lwowski, R. A. deMauriac, R. A. Murray, and L. Lunow, *Tetrahedron Lett.*, 425 (1971); (b) D. G. Morris, B. W. Smith, and R. J. Wood, *Chem. Commun.*, 1134 (1968).
26. P. Robson and P. R. H. Speakman, *J. Chem. Soc., B*, 463 (1968).
27. (a) J. Epsztajn and A. R. Katritzky, *Tetrahedron Lett.*, 4739 (1969); (b) E. A. Sedor, *Tetrahedron Lett.*, 323 (1971).
28. (a) J. Streith and J. M. Cassal, *Angew. Chem., Int. Ed. Engl.*, 7, 129 (1969); (b) J. Streith and J. M. Cassal, *Tetrahedron Lett.*, 4541 (1968); (c) T. Sasaki, K. Kanematsu, and A. Kakehi, *Chem. Commun.*, 432 (1969).
29. (a) T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron*, 28, 1469 (1972); (b) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, 36, 2978 (1971).
30. R. F. Smith, T. A. Craig, T. C. Rosenthal, and R. F. Oot, *J. Org. Chem.*, 41, 1555 (1976).
31. M. Asscher, *J. Org. Chem.*, 41, 715 (1976).
32. J. Garapon and B. Sillion, *Bull. Soc. Chim. Fr.*, 2677 (1975).
33. R. F. Smith and T. A. Craig, *Tetrahedron Lett.*, 3941 (1973).
34. D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, and A. R. Walley, *J. Am. Chem. Soc.*, 98, 292 (1976).
35. (a) J. McKenna, *Tetrahedron*, 30, 1555 (1974); (b) reference 34, footnote 6.

may be essential to its toxic effect.⁴ Others, working with "wildfire" toxin and an apparently identical toxin from *P. coronafaciens*, found some evidence that there were two toxins, one with R = Threonine $\tilde{2}$, and the other with R = Serine $\tilde{3}$.⁷ This was confirmed by Taylor and co-workers who obtained from an unidentified *Pseudomonas* species chlorosis-inducing toxins that had the same amino acid composition and chromatographic behavior as toxins from *P. tabacii* and *P. coronafaciens*. In addition to $\tilde{2}$ and $\tilde{3}$, they obtained $\tilde{4}$ and $\tilde{5}$, which are isomeric, respectively, with $\tilde{2}$ and $\tilde{3}$ and the δ -lactam $\tilde{6}$. These last three compounds were found not to induce chlorosis.⁸



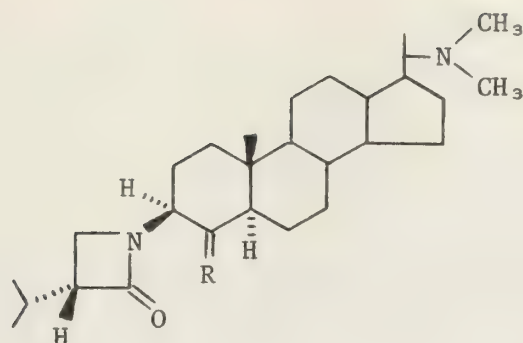
- $\tilde{4}$ R = Threonine
 $\tilde{5}$ R = Serine
 $\tilde{6}$ R = $-\text{CO}_2\text{H}$

It is also worth noting that a compound (S)-alanyl-3-[α (S)-chloro-3-(S)-hydroxy-2-oxo-3-azetidinylmethyl]-(S)-alanine ($\tilde{7}$), similar in structure in structure to "wildfire" toxin, has been isolated from an unknown *Streptomyces* species and has been found to inhibit the growth of several types of Gram negative and Gram positive bacteria.⁹



The bleomycins and phleomycins which comprise a group of related glycopeptide antitumor antibiotics of high therapeutic index have a monocyclic β -lactam moiety in their structures.¹⁰ The total syntheses of these antibiotics have been initiated only recently.¹¹

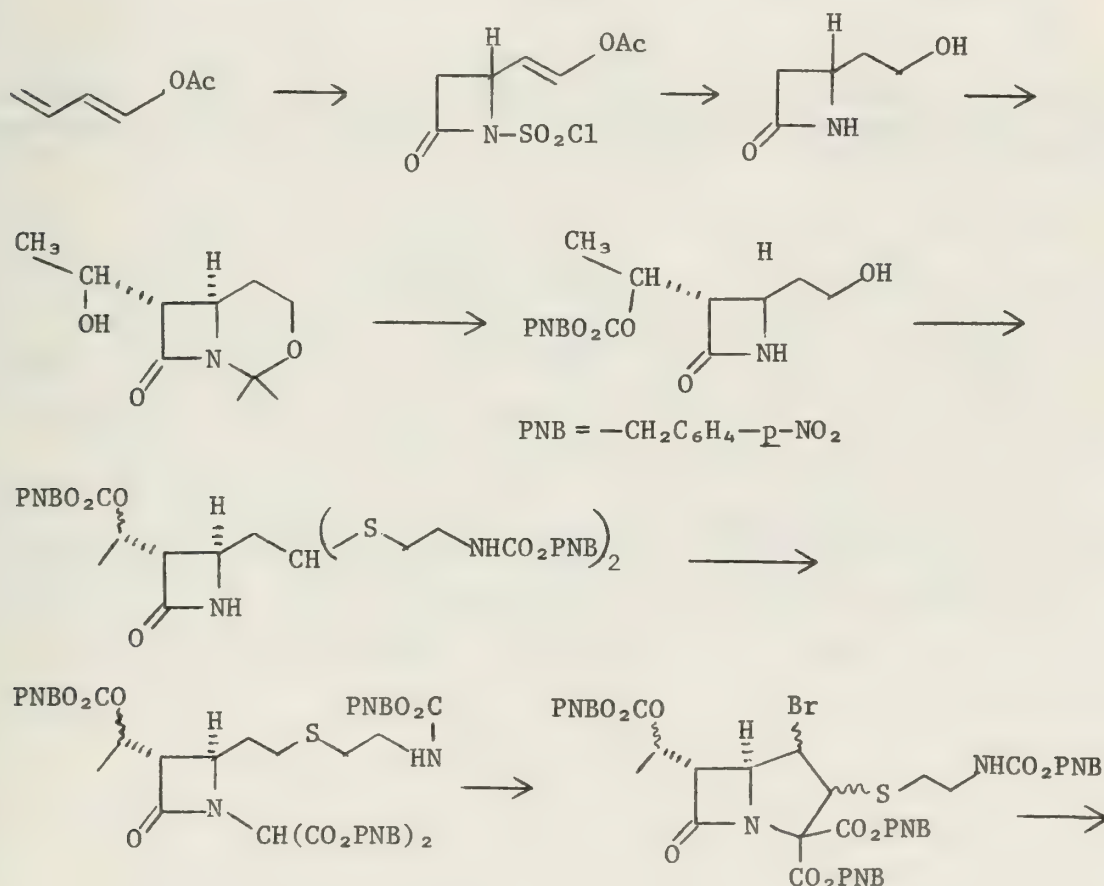
The pachystermines $\tilde{8}$ and $\tilde{9}$ obtained from *Pachysandra terminalis* represent the first and so far the only reported steroidal alkaloids containing a β -lactam moiety.¹² No biological evaluation of these compounds has yet been made.

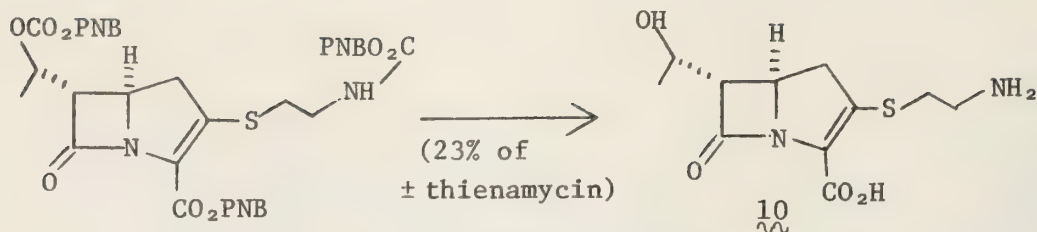


8 R = O

9 R = OH(β); H(α)

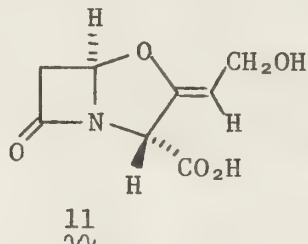
More recently, other compounds have been reported which, although they have some similarity to penicillins and cephalosporins, are nonetheless different from the latter with respect to the fused ring nucleus and side chains. Thienamycin (10) is a broad-spectrum and highly potent antibiotic produced by *Streptomyces cattleya*. The structure of the antibiotic has been determined,¹³ and its total synthesis has been achieved.¹⁴ A scheme for the total synthesis is shown below:



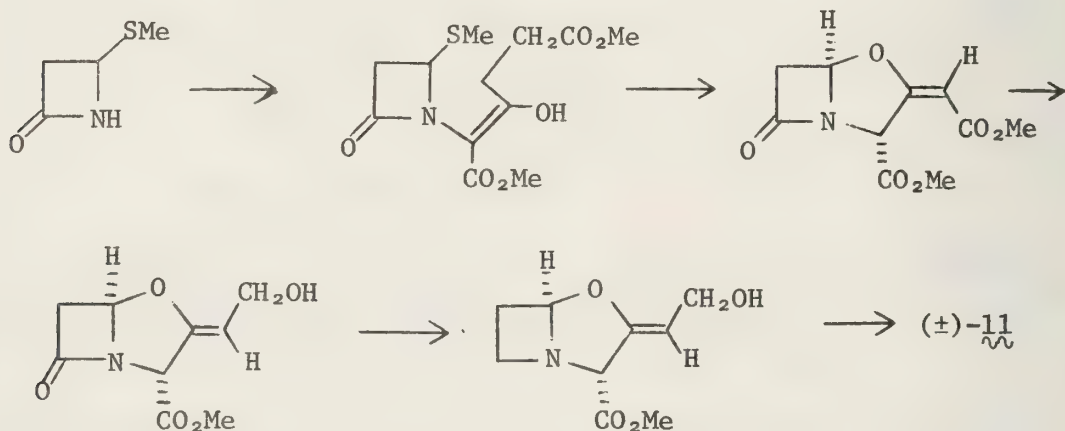


From *Streptomyces flavogriseus* have been isolated other antibiotics which are structurally related to 10 in that they are epimeric to thienamycin at at least one of the asymmetric centers and have structural differences in the side chain.¹⁵

Clavulanic acid (11), which has an oxazolidine ring fused to a β -lactam ring, has been isolated from *Streptomyces clavuligerus*.^{16a,b} It has been shown to possess only weak antibacterial activity;^{16c} however, its potent β -lactamase inhibitory properties against a wide variety of



enzymes^{16c,d} has aroused interest culminating in the total synthesis of this compound and its analogues.^{16e,f} A scheme for the total synthesis is shown below:



BIBLIOGRAPHY

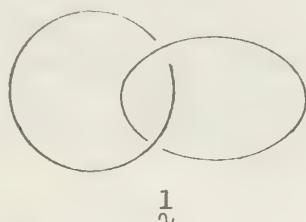
1. H. Aoki, H. Sakai, M. Kohsaka, T. Konomi, J. Hosoda, Y. Kubochi, E. Iguchi, and H. Imanaka, *J. Antibiotics*, 29, 492 (1976).
2. M. Hashimoto, T. Komori, and T. Kamiya, *J. Antibiotics*, 29, 890 (1976).
3. (a) M. Nishida, Y. Mine, S. Nonoyama, H. Kojo, S. Goto, and S. Kuwahara, *J. Antibiotics*, 30, 917 (1977); (b) H. Kojo, Y. Mine, M. Nishida, and T. Yokota, *J. Antibiotics*, 30, 929 (1977); (c) Y. Mine, S. Monoyama, H. Kojo, S. Fukada, M. Nishida, S. Goto, and S. Kuwahara, *J. Antibiotics*, 30, 932 (1977); (d) Y. Mine, S. Nonoyama, H. Kojo, S. Fukada, M. Nishida, S. Goto, and S. Kuwahara, *J. Antibiotics*, 30, 938 (1977).
4. W. W. Stewart, *Nature*, 229, 174 (1971).
5. A. C. Braun, *Phytopathology*, 45, 659 (1955); L. S. Sinden, R. D. Durbin, T. F. Uchytel, and C. Lamar, Jr., *Toxicol. Appl. Pharmacol.*, 14, 82 (1969).
6. A. C. Braun, *Proc. US Nat. Acad. Sci.*, 36, 423 (1950).
7. S. L. Sinden and R. D. Durbin, *Phytopathology*, 60, 360 (1970).
8. P. A. Taylor, H. K. Schnoes, and R. D. Durbin, *Biochem. Biophys. Acta*, 286, 107 (1972).
9. J. P. Scannell, D. L. Pruess, J. F. Blount, H. A. Ax, M. Kellett, F. Weiss, T. C. Demny, T. H. Williams, and A. Stempel, *J. Antibiotics*, 28, 1 (1975).
10. T. Takita, Y. Muraoka, T. Yoshioka, A. Fujii, K. Maeda, H. Umezawa, *J. Antibiotics*, 25, 755 (1972).
11. D. A. McGowan, U. Jordis, D. K. Minster, S. M. Hecht, *J. Am. Chem. Soc.*, 99, 8078 (1977).
12. T. Kikuchi and S. Uyeo, *Chem. Pharm. Bull.*, 15, 549 (1967).
13. G. Albers-Schönberg, B. H. Arison, E. Kaczka, F. M. Kahan, J. S. Kahan, B. Lago, W. M. Maiese, R. E. Rhodes, and J. L. Smith, 16th Intersci. Conf. of Antimicro. Ag. and Chemother. Abstract, 229 (1976); U. S. Patent 3,950,357, CA, 85, 92190t (1976).
14. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, G. B. Christensen, *J. Am. Chem. Soc.*, 100, 313 (1978).
15. P. J. Cassidy, E. O. Stapley, R. Goegelman, T. W. Miller, B. Arison, G. Albers-Schönberg, S. B. Zimmerman, and J. Birnbaum, 17th Intersci. Conf. on Antimicro. Ag. and Chemother. Abstract, 81 (1977).
16. (a) T. T. Hawarth, A. G. Brown, T. J. King, *J. Chem. Soc., Chem. Commun.*, 266 (1976); German Patent 2,517,316; (b) C. Reading and M. Cole, *Antimicro. Ag. and Chemother.*, 11, 852 (1977); (c) P. A. Hunter and C. Reading, 16th Intersci. Conf. on Antimicro. Ag. and Chemother. Abstract, 211 (1976); J. Wüst and T. D. Wilkins, *Antimicro. Ag. and Chemother.*, 13, 130 (1978); (e) P. H. Bentley, P. D. Berry, G. Brook, M. L. Gilpin, E. Hunt, and I. I. Zomaya, *J. Chem. Soc., Chem. Commun.*, 748 (1977); (f) P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *J. Chem. Soc., Chem. Commun.*, 905 (1977).

THE SYNTHESIS AND CHARACTERIZATION OF CATENANES

Reported by James L. Schreiner

March 27, 1978

Background. Throughout the years, organic chemists have been interested in synthesizing compounds that have not (or not yet) been found in Nature. In the early 1900's Willstätter, speaking at a seminar in Zürich, mentioned a compound that consists of two separate fragments not linked by a chemical bond.¹ Statistical calculations indicate that complex cyclic systems of this type can be formed.² The type of compound mentioned by Willstätter was later called a catenane \int (Latin: catena = chain).³ Catenane compounds are topological isomers of all the macrocycles in them.



The work of Ziegler *et al.*,⁴ Hansley,⁵ Prelog *et al.*,⁶ and Stoll *et al.*,⁷ on the synthesis of macrocyclic compounds between 1930 and 1950 gave the impetus for attempting the synthesis of catenanes. The size of the macrocycle needed to allow a methylene group to pass through it was the object of molecular model calculations. Stuart-Briegleb molecular models show that [2]-Catenanes can be constructed with macrocycles consisting of at least 18 methylene groups.¹ On the other hand, Fischer-Hirschfield molecular models, which take into account interatomic repulsions, set the minimum ring size at 20 methylene groups.⁸

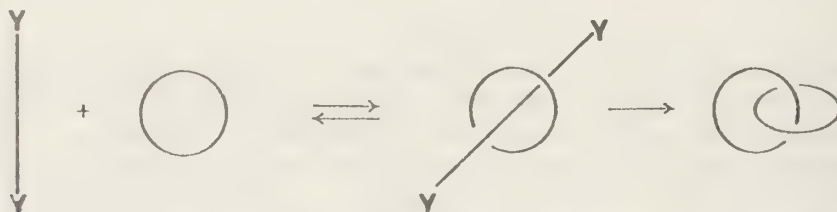
The first isolation of a catenane was reported by Wasserman in 1960.³ However, the major research on the synthesis of catenanes was designed and attempted in the laboratories of Lüttringhaus at the University of Freiburg beginning in the late 1950's. More recently, major research on the synthesis of catenanes has been done by his former students Schill and Isele, also at the University of Freiburg.

A method for naming catenanes was proposed in 1971 by Schill.¹ The number of rings comprising the catenane is placed in brackets and precedes the name. IUPAC nomenclature is used to identify the macrocyclic subunits of the catenane. After these names, the word "catenane" is placed. If there is a multiple winding, the winding number (α)⁹ is placed following the entire name. Introduction of the topological bonding number (TBN) by Hudson and Vinograd can also be used effectively.⁹ The TBN describes the number of rings that need to be opened to release a particular ring. A catenane is described by the TBN, for each ring in them.

Synthetic Pathways. The synthesis of catenanes can be divided into three main types. The first type, the statistical pathway, allows statistical law to control the amount of catenane that is formed. Formation of the catenanes is accomplished, but the yields are low. The second type, the directed synthesis, uses sterically influenced precursors that prefer formation of the catenane. The final type, the Möbius strip method, relies on the theory of the Möbius strip to form first the precursor, then the catenane.

Statistical Synthesis. The statistical pathway can be divided into five schemes, four envisioned by Lüttringhaus¹⁰ and the fifth, by Schill.¹ Differences between the five schemes are limited usually to the placement and the number of auxiliary linkages. An auxiliary linkage is a chemical bond that is used to influence the statistical laws that govern the reaction and is later cleaved to produce the catenane.

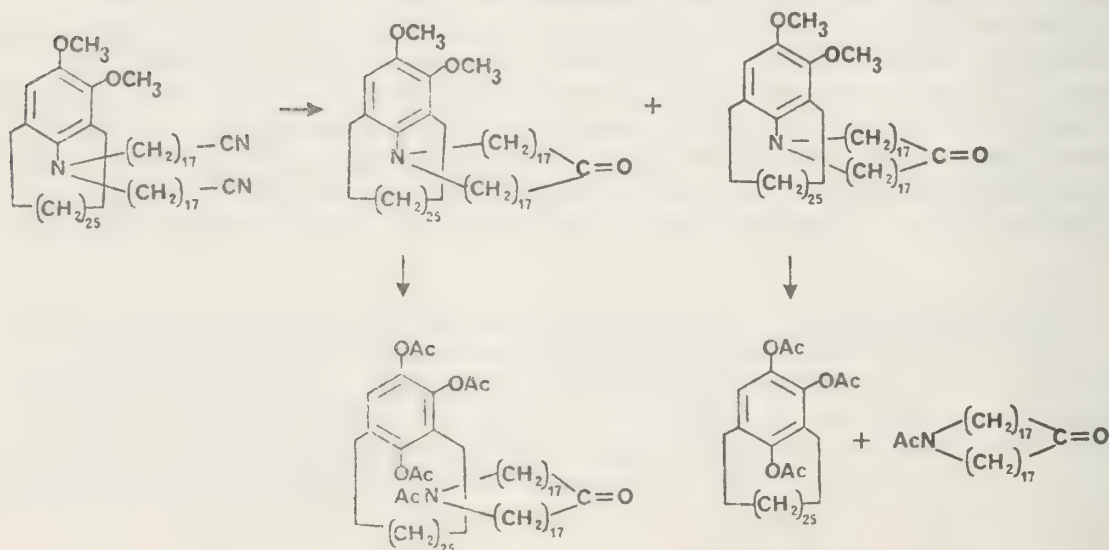
Scheme I involves the statistical equilibrium between a non-contained long chain and a contained long chain, in a preformed macrocycle. This is the method that Wasserman used in the first synthesis of a catenane.³ He isolated "a few milligrams" of a substance in 0.0001% yield based on the starting material, sebacic acid.^{1,11} The low yield is due to the low equilibrium concentration of the contained long chain. Wasserman caused diethyl tetratriacontanedioate to undergo an acyloin condensation in the presence of a 1:1 mixture of xylene and a deuterated cycloparaffin. The deuterated cycloparaffin is cyclotetratriacontane that contains, on the average, five deuterium atoms per molecule. The catenane was separated from the macrocyclic subunits and characterized by analysis of the degradative products of the catenane.

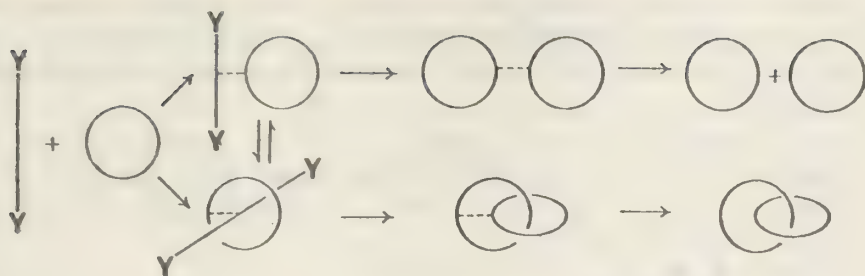


Scheme I

Scheme II uses an auxiliary linkage between the long chain and the macrocycle to influence the statistical law. Again, there is an equilibrium established between the contained and non-contained long chain. The contained compound that is closed, but still has the auxiliary linkage present, is called a precatenane. Lüttringhaus and his co-workers have used this scheme in many cases.^{1,10} A successful application of this method is seen in Figure 1 from the work of Lüttringhaus and Isele.¹²

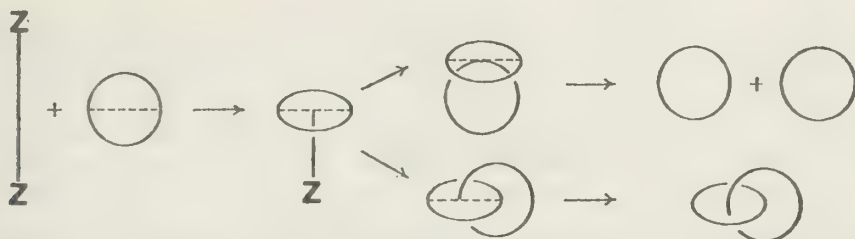
Figure 1





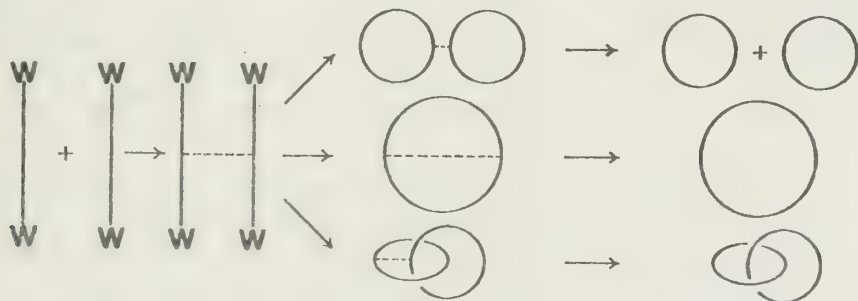
Scheme II

Scheme III has an intraannular bridge in the macrocycle as its auxiliary linkage. The long chain compound has one end bound to the intraannular bridge and the other end free. Cyclization gives either a precatenane or a compound that upon cleavage of the auxiliary linkages gives the macrocyclic subunits. Investigations of this scheme have been unsuccessful, primarily due to the inability to form macrocyclic sulfonium or ammonium salts.¹



Scheme III

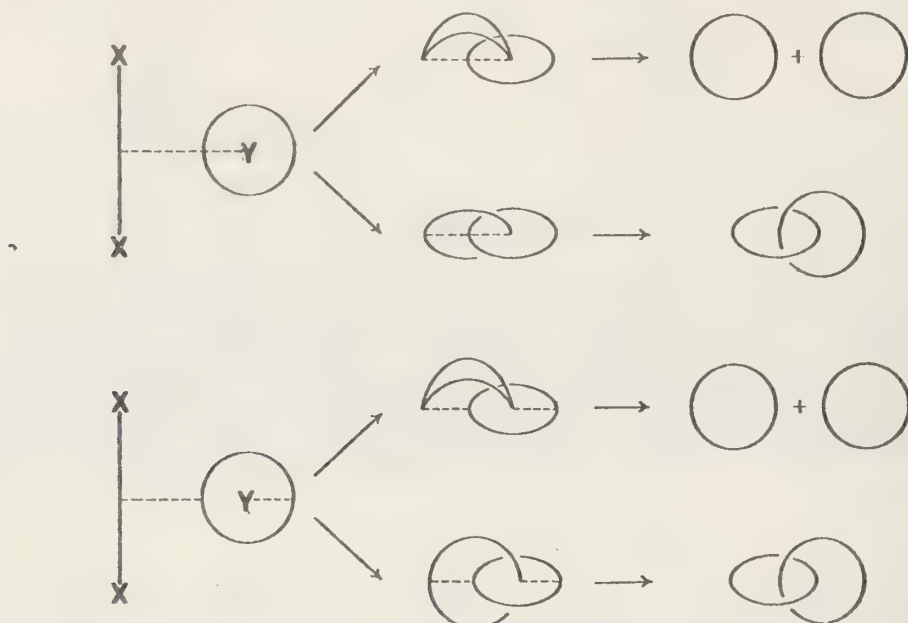
Scheme IV has an auxiliary linkage between two long chain compounds. Cyclization followed by cleavage of the auxiliary linkage affords three compounds. As in the other statistical schemes, a catenane and its macrocyclic subunits are formed. In addition, a macrocycle is formed from closure of the long chains with each other. Early attempts to use this scheme resulted in the conclusion that only the large macrocycle was being formed.



Scheme IV

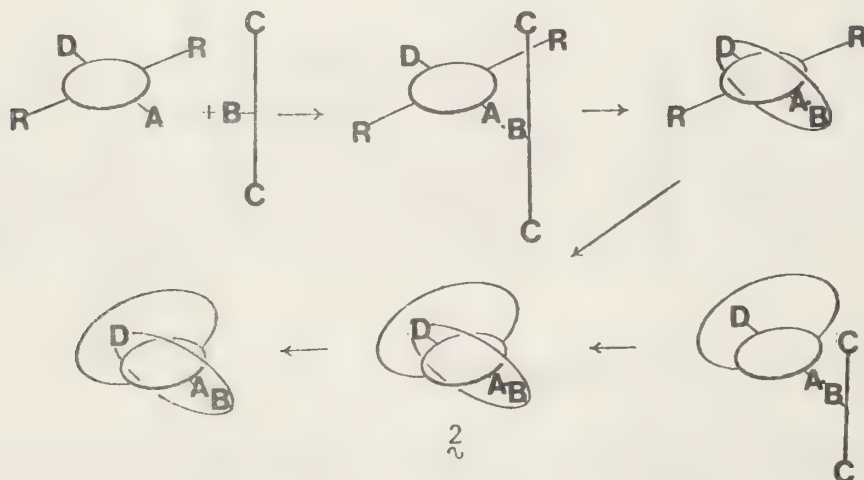
Scheme V, although first described by Schill,¹³ was also attempted by Lüttringhaus and co-workers.¹ This scheme uses multiple auxiliary linkages to influence further the statistical distribution of products. One auxiliary linkage is between the preformed macrocycle and a functional

group onto which the long chain can cyclize. The other linkage is between the long chain and the preformed macrocycle. Difficulties were encountered when attempts were made to synthesize catenanes using this scheme.



Scheme V

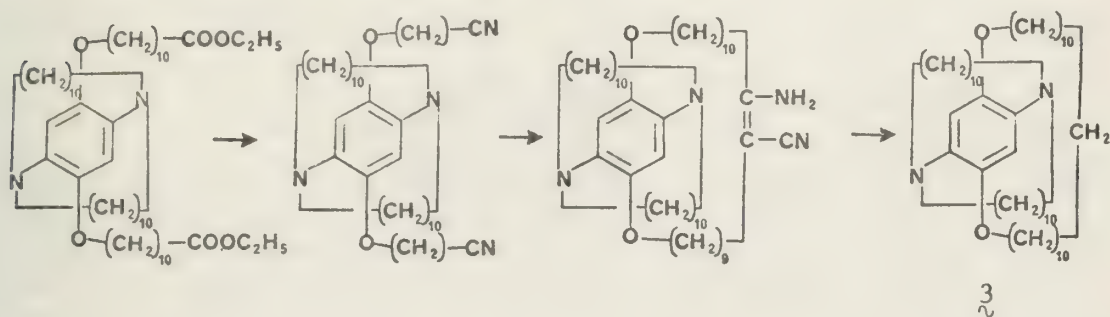
Directed Synthesis. Statistical schemes have given catenanes in low yields or no catenanes were formed. Realizing the need for a different method, Schill described a method to form precatenanes that was not affected substantially by statistical probabilities.^{1,14} This method is called "directed synthesis", and has become the most widely used method. Initial investigations were undertaken to determine the possibility of formation of the triansa compound 2 . Scheme VI shows two different routes for the preparation of a triansa compound. Cleavage of the bonds between A and B and between the planar ring and D yields the desired catenane.



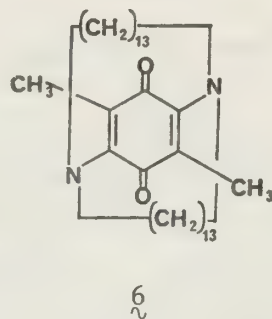
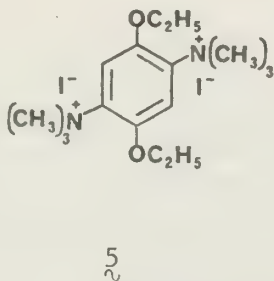
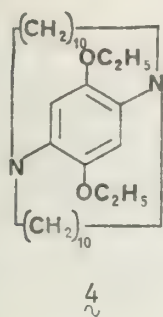
Scheme VI

Doornbos and Strating prepared a triansa compound by forming a third ring on an existing diansa compound.^{1,15} Figure 2 illustrates the route that they followed. Acyloin condensation failed on the diester, but the dinitrile could be closed. The triansa compound $\tilde{3}$ was identical to the compound Schill prepared by an alternate route. To obtain a catenane, cleavage of the aryl-nitrogen bond is required. Three methods were considered for the cleavage step.

Figure 2



Birch reduction, using sodium in liquid ammonia, on the model compound $\tilde{4}$ was unsuccessful, and starting material was recovered.¹⁶ The second method tried was electrolysis of quaternary phenylammonium salts. The reaction of methyl iodide with compound $\tilde{4}$ at room temperature gave the monomethiodide, which could not be purified. Reaction at 90°C during 70 hrs. resulted in trans-alkylative formation of 1,10-diiododecane and the bis-quaternary ammonium salt $\tilde{5}$. It was believed that the benzene ring may have been too sterically hindered to allow close approach to the electrode surface. The final method tried was the catalytic hydrogenolysis of compound $\tilde{4}$ using a poisoned palladium catalyst. Again, no reaction took place on the model compound $\tilde{4}$.

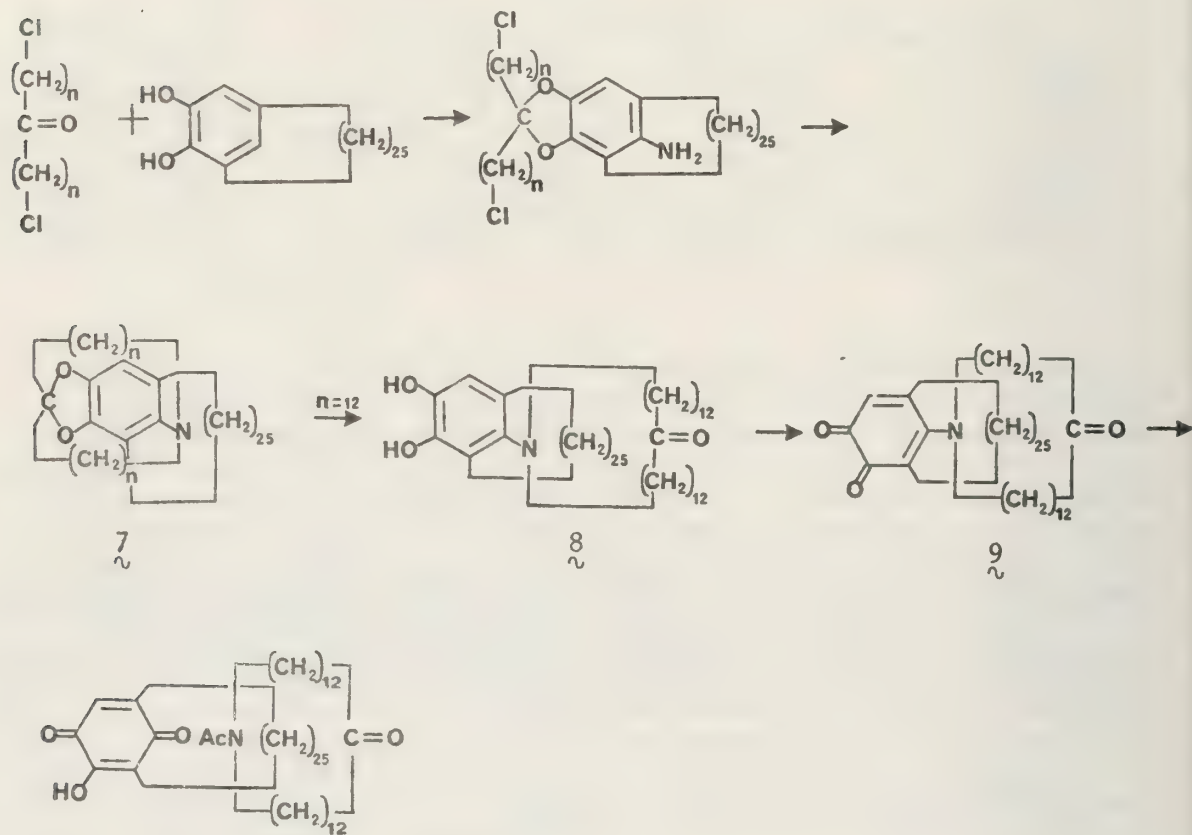


Since cleavage of the aryl-nitrogen bond in model compound $\tilde{4}$ was not accomplished, a different type of triansa compound was sought. Two systems were studied: (1) hydrolysis of diamino-p-benzoquinones, and (2) hydrolysis of amino-o-benzoquinones. The first system was studied on the model compound $\tilde{6}$, by Schill and Neubauer.¹⁸ Conversion of the diether to the p-benzoquinone followed by hydrolysis yielded a dihydroxybenzoquinone and a macroheterocycle.¹⁸ The use of this method of cleavage to form a catenane has not been successful to date.

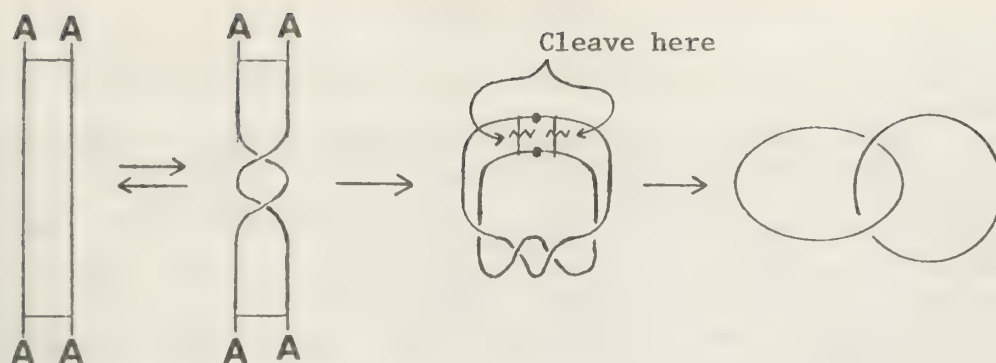
The second method of preparing a triansa compound is to add two rings to an existing monoansa compound. Schill prepared the triansa compound $\tilde{7}$ using this route.¹⁹ The synthetic route is depicted in

Figure 3. Hydrolysis of the ketal linkage was effected for $n=12$, using hydrobromic acid in acetic acid or propionic acid.¹⁹ Only when drastic conditions are used is the ketal linkage cleaved for $n=10$, but hydrolysis is then accompanied by cleavage of the N-methylene bond.^{1,20} Subsequent dehydrogenation of the amino-catechol **8**, with $n=12$, followed by acid hydrolysis of the amino-o-benzoquinone **9** leads to a catenane.

Figure 3



Möbius Strip Method. The final synthetic route uses the Möbius Strip theory and is outlined in Scheme VII. Formation of a catenane and some of its topological isomers was postulated for the metathesis reaction of cyclic olefins.²¹ Mass spectral confirmation of a catenane from the metathesis reaction of cyclododecene was reported by two independent laboratories at nearly the same time.²²



Scheme VII

Characterization. Characterization of a catenane is aided by having an authentic sample of the molecular subunits of the catenane. After separation of the proposed catenane from the reactants by chromatography, Wasserman used degradation to help identify the catenane. Oxidative cleavage of the catenane gave two compounds. One had identical melting point, chromatographic behavior, and infrared spectrum as the starting deuterated macrocycle. Also, no lowering of the melting point was observed when a mixed melting point was taken. The other compound obtained was identical to the diacid from which the starting diester was derived. The proposed catenane exhibited an infrared band corresponding to C-D stretching.

Isothermal distillation can be used to check the molecular weight.²³ The results must correlate with the proposed structure and be within the limits of this method. Since no change has been made in the bonds of the macrocyclic subunits when they exist as a catenane, the infrared spectra should be identical or show only slight changes due to van der Waals interactions.

If the molecular weight of the catenane is not too high, a mass spectrum can be obtained. A molecular ion peak may be present with an m/e corresponding to the sum of the macrocyclic subunits contained.^{24,25} Peaks will appear at higher m/e values than either of the molecular subunits that will correspond to ions that form either without ring opening or form intramolecular ion reactions, such as a hydrogen transfer.²⁴

NMR differences between a catenane and a 1:1 mixture of the molecular subunits are not large. ^{13}C NMR shows a downfield shift for the resonances of the catenane compared with the resonances from the mixture of subunits. The downfield shift has been attributed to a decrease in the γ -gauche interactions.²⁶ ^1H NMR exhibits both upfield and downfield shifts in the resonances of the catenane with respect to the macrocyclic components. These shifts are thought to arise from solvent interactions with the catenane and are not very well understood.

BIBLIOGRAPHY

1. G. Schill, "Catenanes, Rotaxanes, and Knots," Academic Press, New York, N.Y., 1971.
2. H. L. Frisch and E. Wasserman, J. Am. Chem. Soc., 83, 3789 (1961).
3. E. Wasserman, *ibid.*, 82, 4433 (1960).
4. K. Ziegler and W. Hechelhammer, Justus Liebigs Ann. Chem., 528, 114 (1937), and references therein.
5. (a) V. L. Hansley, J. Am. Chem. Soc., 57, 2303 (1935); (b) V. L. Hansley, U.S. Patent 2,228,268 (1941).
6. V. Prelog, L. Frenkiel, M. Kobelt, and P. Barmon, Helv. Chim. Acta, 30, 1741 (1947).
7. (a) M. Stoll and A. Rouvé, *ibid.*, 30, 1822 (1947); (b) M. Stoll and J. Hulstkamp, *ibid.*, 30, 1815 (1947).
8. E. A. Mason, J. Chem. Phys., 23, 49 (1955).
9. B. Hudson and J. Vinograd, Nature (London), 216, 647 (1967).
10. (a) A. Lüttringhaus, F. Cramer, H. Prinzbach, and F. M. Henglein, Justus Liebigs Ann. Chem., 613, 185 (1958); (b) A. Lüttringhaus, F. Cramer, and H. Prinzbach, Angew. Chem., 60, 137 (1957).
11. E. Wasserman, Sci. Amer., 207, 94 (1962).
12. A. Lüttringhaus and G. Isele, Angew. Chem., Int. Ed., English, 6, 956 (1967).
13. G. Schill, Habilitation Thesis, University of Freiburg, Freiburg, Germany, 1964.
14. G. Schill, Chem. Ber., 98, 2906 (1965).
15. T. Doornbos and J. Strating, Rec. Trav. Chim. Pays-Bas, 85, 41 (1966).
16. G. Schill, Chem. Ber., 98, 3439 (1965).
17. Schill also prepared triansa compound $\frac{4}{\Delta}$ using the second method, as opposed to the first method used by Doornbos and Strating.^{13,14}
18. G. Schill and H. Neubauer, Justus Liebigs Ann. Chem., 750, 76 (1971).
19. G. Schill, Chem. Ber., 100, 2021 (1967).
20. G. Schill, Justus Liebigs Ann. Chem., 695, 65 (1966).
21. E. Wasserman, D. A. Ben-Efraim, and R. Wolovsky, J. Am. Chem. Soc., 90, 3286 (1968).
22. (a) R. Wolovsky, *ibid.*, 92, 2132 (1970); (b) D. A. Ben-Efraim, C. Batich, and E. Wasserman, *ibid.*, 92, 2133 (1970).
23. H. Hoyer, Angew. Chem., 73, 465 (1961).
24. G. Schill and W. Vetter, Tetrahedron, 3079 (1967).
25. G. Agam and A. Zilka, J. Am. Chem. Soc., 98, 5214 (1976).
26. H. Fritz, E. Logemann, G. Schill, and T. Winkler, Chem. Ber., 109, 1258 (1976).

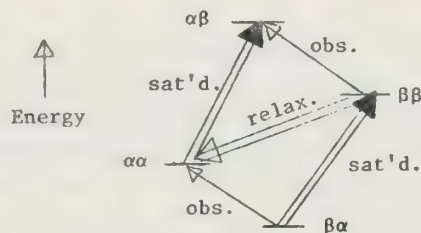
THEORY AND APPLICATIONS OF ^{15}N NMR

Reported by Kirk A. Simmons

March 30, 1978

Nitrogen in some form has the potential of participating directly in fundamental biological and chemical processes.¹ For this reason, ^{15}N nuclear magnetic resonance is an attractive method for the study of nitrogen within organic compounds. In spite of the fact that ^{15}N has a spin quantum number of $1/2$ and hence gives rise to sharp resonances ($W_{1,2} < 5$ hz.), its detection is far from routine. The reasons are the low natural abundance of ^{15}N (0.365%) and the negative magnetogyric ratio (-0.1013 relative to ^1H).² The sensitivity of ^{15}N relative to ^{13}C in an NMR experiment with both nuclei at their natural abundance is approximately 1:30.¹ Thus, ^{15}N would require about 900 times longer than ^{13}C to provide a spectrum of similar signal-to-noise ratio. Larger sample volumes (25 mm tube diameter) and advances in instrumentation have yielded a gain of about 20X for the detection of ^{15}N .¹ The negative magnetogyric ratio, however, is still a major drawback, seriously impeding an application of proton decoupling for signal enhancement. An intensity effect known as the Nuclear Overhauser Enhancement (NOE) occurs during the decoupling experiment. The NOE can be defined, as for all nuclei, as the ratio of the signal intensity with decoupling to the signal intensity without decoupling. Figure 1 shows an energy level diagram for an AX decoupled spin system when the magnetogyric ratios for the two nuclei are opposite in sign.³ In the

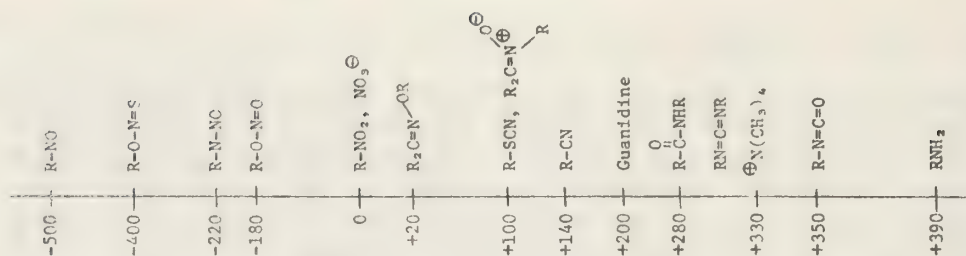
Figure 1. Energy levels for an AX spin system



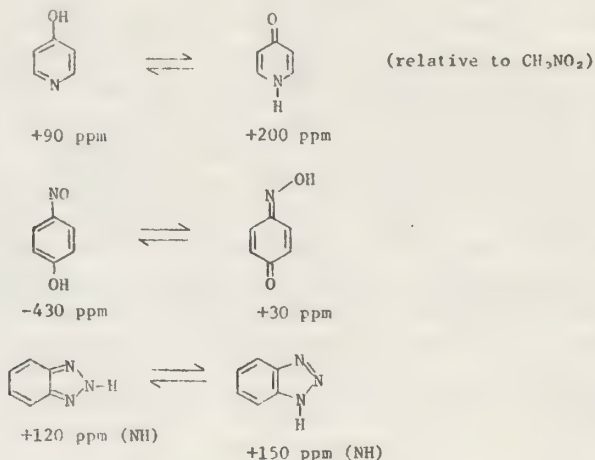
pairs of spin labels the first term refers to the ^{15}N and the second term refers to the ^1H nucleus. The decoupling experiment, *i.e.*, saturation of the ^1H resonances, equilibrates the populations between states $\alpha\alpha, \alpha\beta$ and $\beta\alpha, \beta\beta$. When dipole-dipole interaction between the ^{15}N nucleus and the ^1H nucleus is the dominant relaxation pathway, the populations in the energy levels $\beta\beta$ and $\alpha\alpha$ are equilibrated.⁴ The net result is that the excited state energy levels ($\alpha\alpha$ and $\alpha\beta$) are being overpopulated in the Boltzmann sense at the expense of their ground states ($\beta\alpha$ and $\beta\beta$). The intensity of the nmr signal depends on this population difference and since the population difference ($P_{\text{g.s.}} - P_{\text{E.S.}}$) is negative one observes an emission signal, *i.e.*, an inverted signal, when passing through resonance.

Chemical shifts of nitrogen cover an astonishing spectral range of 900 ppm compared to 200 ppm for ^{13}C and 20 ppm for ^1H . This is one appealing feature of ^{15}N NMR. Figure 2 shows resonance positions for some organic compounds.⁵

Figure 2. ^{15}N spectral range



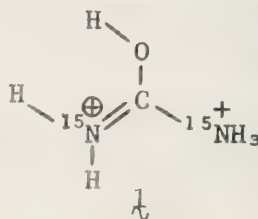
Nitrogens involved in tautomeric equilibria undergo large changes in their chemical shift position.⁵



Characteristic functional group chemical shifts, absence of ^{13}C - ^{13}C coupling, simplicity of the resulting ^1H decoupled spectra, well-defined substituent parameters, and a favorable nuclear Overhauser enhancement have allowed natural abundance ^{13}C NMR to achieve the widespread use it now enjoys.⁶ In an effort to bring ^{15}N NMR to the same level, considerable work has been concentrated on the problem aspects.^{1, 5, 7, 8-14} Experimental and theoretical study has shown correlations between nitrogen-proton coupling constants and molecular structure.^{11-13, 15-17} The 1J ($^{15}\text{N-H}$) linearly correlates to the hybridization of the nitrogen. Empirical formulas similar to those obtained for ^{13}C ⁶ have been presented relating the magnitudes of 1J ($^{15}\text{N-H}$) to the %s character of the nitrogen-hydrogen bond, Eq. 1 and Eq. 2.

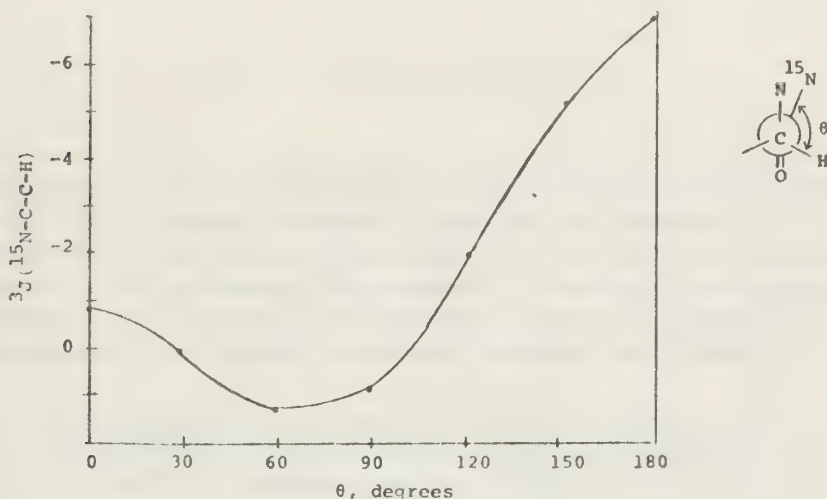
$$\begin{aligned} \text{\%s character} &= 0.43 \text{ } ^1J \text{ (} ^{15}\text{N-H) - 6} & (1) \\ \text{\%s character} &= 0.34 \text{ } ^1J \text{ (} ^{15}\text{N-H)} & (2) \end{aligned}$$

An example of the use of such information is the work of Olah and White.¹⁸ These workers studied the protonation of doubly-labeled ^{15}N urea in strong acid ($\text{FSO}_3\text{H}/\text{SbF}_6/\text{SO}_2$) at low temperature and found evidence for a diprotonated species with non-equivalent nitrogens. Based on the two observed one-bond $^{15}\text{N-H}$ coupling constants of 76.6 and 96.8 Hz, structure was proposed.



Two-bond coupling between nitrogen and hydrogen is generally small through a saturated system, $^2J(^{15}\text{N}-\text{H}) \sim 1 \text{ Hz}$, and larger through an unsaturated linkage, $^2J(^{15}\text{N}=\text{H}) \sim 10\text{-}25 \text{ Hz}$.² Three-bond coupling may prove to be diagnostic of conformational structure in solution since $^3J(^{15}\text{N}-\text{C}-\text{C}-\text{H})$ follows a relationship similar to the Karplus-relation in ^1H NMR^{15,16} (Figure 3).

Figure 3. Karplus Relation for $^3J(^{15}\text{N}-\text{C}-\text{C}-\text{H})$



The accumulation of ^{15}N NMR shifts for amines^{6,14} has allowed the calculation of substituent parameters. After obtaining shift data on both primary and secondary amines, the substituent parameters, Table 1, were obtained via linear regression analysis using the chemical shift position (upfield from H^{15}NO_3) of $^{15}\text{NH}_3$ for the constant C.

Table 1. Substituent Parameters for 1° Amines

α	-8.7 ppm
β	-18.2 ppm
γ	+2.7 ppm
δ	-3.0 ppm
ϵ	+1.8 ppm
C	379 ppm

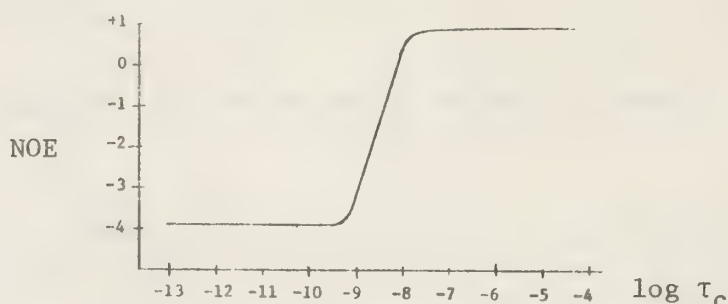
Deshielding α and β effects, shielding (presumably due to steric interactions) γ effects and deshielding δ effects for ^{15}N are reminiscent of similar findings in ^{13}C NMR.^{6,7}

Substituent effects for amines correlate well with analogous effects in the corresponding hydrocarbon ^{13}C spectra based on a linear relationship when $\delta^{15}\text{N}$ values are plotted against $\delta^{13}\text{C}$ values in the analogous hydrocarbon. This indicates that the cause of substituent-induced chemical-shift changes may be common to ^{15}N and ^{13}C .

Even though the negative NOE for ^{15}N is a problem, its dependence on the correlation time, τ_c , of a molecule allows one to gain further insight into molecular motion in solution. τ_c is effectively the time

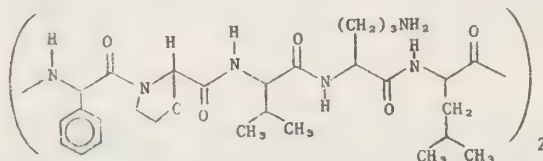
constant for molecular reorientation. Figure 4 shows the dependence of the NOE for ^{15}N as a function of τ_c .^{1,8,19}

Figure 4. ^{15}N NOE vs. $\log \tau_c$



The main feature to note in Figure 4 is for fast molecular motion ($\tau_c < 10^{-9}$ s) the NOE attains its maximum value of -3.93 while for slower motion ($\tau_c > 10^{-8}$ s) the NOE is +0.88. In the range of 10^{-9} s to 10^{-8} s the value of the NOE varies from negative through zero to positive. This dependence has been utilized by Hawkes and coworkers⁸ in their natural abundance ^{15}N study of the decapeptide Gramicidin S, cyclo-(D-Phe-L-Pro-L-Val-L-Orn-L-Leu)₂, the partial structure of which is presented in Figure 5.

Figure 5. Partial structure of Gramicidins



The backbone amide resonances occur in the region of 90-120 ppm downfield from $^{15}\text{NH}_4\text{NO}_3$. When the spectrum was accumulated (36 h) in $(\text{CD}_3)_2\text{SO}$ (0.3 M) no amide resonances could be found. From the line widths of the ^{13}C methine carbon resonances the correlation time in $(\text{CD}_3)_2\text{SO}$ (0.3 M) was calculated as 5.4×10^{-9} s, the necessary time for the NOE to be near zero. To confirm this observation the $(\text{CD}_3)_2\text{SO}$ solution was diluted with CH_3OH (1:4). This reduced the viscosity, thereby shortening the correlation time so that the ^{15}N spectrum now shows the amide resonances. In fact, in CH_3OH alone (0.2 M) the correlation time is sufficiently shortened for a full negative NOE (-3.93) to be observed. The correlation time in CH_3OH was estimated as 6×10^{-10} s using the ^{13}C line widths. The amide resonances also appeared simply by warming the original $(\text{CD}_3)_2\text{SO}$ solution (from 18° C to 47° C), thereby reducing τ_c .

Applications

Much of the early investigation using ^{15}N NMR dealt with the amino acids²⁰⁻²⁴ and peptides^{1,25} in anticipation that information gained could be applied to more complicated biological systems. Roberts and co-workers²⁵ have studied simple peptides to ascertain the effect of sequencing in the peptide upon the nitrogen chemical shifts. Results presented in Table 2 indicate that the chemical shift of the nitrogen in the N-terminal amino acid was essentially independent of the peptide sequence.

Table 2. $\delta^{15}\text{N}$ (relative to $^{15}\text{NH}_4$) for some dipeptides

Peptide	$\delta^{15}\text{N}$ for N-terminal amino acid, ppm
AcGly	$\delta 89.4 \pm 0.3$
AcGlyGly	$\delta 89.1 \pm 0.3$
AcGlyAla	$\delta 89.1 \pm 0.3$
AcGlyLeu	$\delta 89.1 \pm 0.3$
	$\delta^{15}\text{N}$ for C-terminal amino acid, ppm
AcGlyGly	$\delta 84.0 \pm 0.3$
AcAlaGly	$\delta 83.5 \pm 0.3$
AcLeuGly	$\delta 84.6 \pm 0.3$

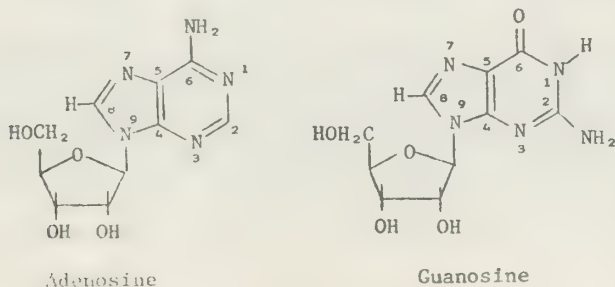
By contrast, the chemical shift of the nitrogen in the C-terminal amino acid is affected by the sequence (Table 2). However, the change in the chemical shift (upfield shift of 5.4 ± 0.5 ppm) is independent of the structure of the N-terminal amino acid, a result similarly concluded using ^{13}C and ^1H NMR.²⁶ Because of this independence, the hope of utilizing ^{15}N NMR to sequence peptides was not realized.

Recently, ^{15}N NMR has been used to deduce the most probable site of protonation in some nucleosides and nucleotides.²⁷ Based on the upfield shift (97 ppm) of the nitrogen of pyridine when trifluoroacetic acid is added, nitrogen resonances shift upfield upon protonation. Table 3 lists the chemical shifts of the nitrogens of adenosine and guanosine, Figure 6, as a function of added trifluoroacetic acid.

Table 3. $\delta^{15}\text{N}$ (relative to D^{15}NO_3) for adenosine and guanosine

Substrate	Mol eq TFA	N1	N3	N7	N9	C_6NH_2
Adenosine	0	139.6	152.7	134.7	205.6	293.8
	0.16	147.0	153.0	135.4	205.0	293.4
	0.31	155.6	152.9	135.3	204.4	292.2
	1.60	211.3	150.8	131.4	197.4	284.9
		N1	N3	N7	N9	C_2NH_2
Guanosine	0	228.0	209.5	128.6	205.3	302.0
	0.17	227.5	209.3	143.6	203.6	300.5
	0.36	227.2	209.9	150.5	203.0	300.0
	1.86	226.0	211.0	194.9	199.4	296.8

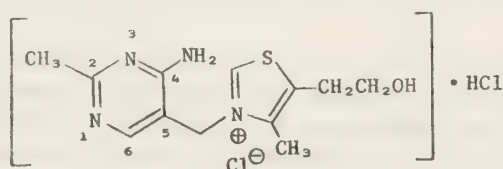
Figure 6. Numbering scheme for adenosine and guanosine



Nitrogen assignments were made on the basis of chemical shifts, one- and two-bond ^{15}N -H coupling constants, and comparison with model compounds. Due to the large upfield shifts experienced by N1 (71.7 ppm) of adenosine and N7 (66.3 ppm) of guanosine, it was concluded that these nitrogens were the predominant site of protonation, in agreement with theory²⁸ and earlier experiments²⁹, including an x-ray structure determination of adenosine hydrochloride.³⁰

Very recently, Roberts and coworkers³¹ have extended their protonation studies to Vitamin B₁ hydrochloride, Figure 7. The ^{15}N NMR

Figure 7. Numbering scheme for Vitamin B₁ (HCl)



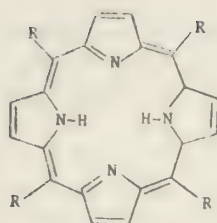
spectrum of thiamine hydrochloride in water solution shows four well-separated resonances: 3 singlets at δ 136, 166, and 208 ppm (relative to H^{15}NO_3) and a triplet at δ 268 ppm. The triplet, $J = 91$ Hz, is assigned the C4 amino group and clearly establishes that this nitrogen is not protonated. Exchange of the thiazole proton with deuterium caused the resonance at δ 136 to sharpen considerably. The thiazole nitrogen is therefore assigned to the δ 136 ppm resonance. Decoupling the C6 proton in D_2O solution caused a sharpening of the resonance at δ 208 ppm. Consistent with this finding and predicted shifts using substituent parameters was the assignment of N1 to the δ 208 resonance. N3 was assigned the resonance at δ 166 since decoupling the pyrimidine methyl group affected this signal. Since vitamin B₁ hydrochloride is dicationic, reaction with sodium hydroxide should lead to deprotonation and effect a downfield shift for the nitrogen undergoing the deprotonation. The effect of base on the chemical shift positions is presented in Table 4. These results suggest that the site of proton-

Table 4. δ ^{15}N for Vitamin B₁ Hydrochloride (relative to H^{15}NO_3)

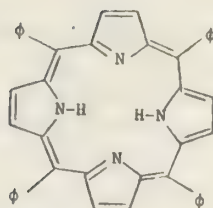
Mol eq ^-OH	C_4NH_2	N3	N1	Thiazole N
0	266.8	164.7	208.8	130.5
0.25	272.2	163.9	189.3	131.2
0.75	280.8	162.8	159	132.8
1.00	288.0	161.8	135	134.0

ation in vitamin B₁ hydrochloride is N1, consistent with other findings.³²

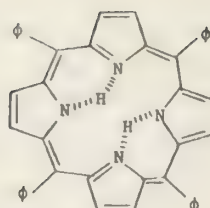
^{15}N NMR results have been reported for the porphyrins^{33, 34} of the general structure shown (2). The protons bonded to the nitrogens undergo intramolecular exchange, and earlier work utilizing $^1\text{H}^{35}$ and $^{13}\text{C}^{36}$ nmr to study this exchange could only suggest, but not differentiate, between the two possible structures 3 and 4 in the region of no exchange (low temperature, -80°C).



2



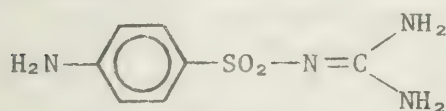
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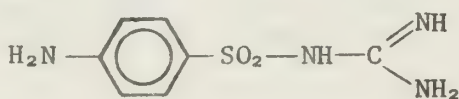
4

At low temperatures, -80°C , two resonances were observed for the β -pyrrole protons and carbons. Upon warming to 30°C , the two signals coalesced to a single resonance. It was possible to distinguish between the two 'frozen structures' by the use of ^{15}N NMR. In structure 3, the nitrogens are in two magnetically different environments and hence should give rise to two signals while in structure 4, all of the nitrogens are equivalent and one should observe only one signal. Although exchange still occurred at -12°C , two ^{15}N resonances, which coalesced to a single resonance at room temperature, were observed at δ 241 ppm and δ 132 ppm (relative to H^{15}NO_3). The observation of two signals at low temperature confirms structure 3 in solution. The resonance at δ 241 ppm was assigned the nitrogens bonding the protons by comparison with pyrrole, δ 233 ppm, and the resonance at δ 132 ppm was assigned the $=\text{N}$ nitrogens.

Only recently has the application of ^{15}N NMR to structure elucidation come about.³⁷⁻⁴⁰ An interesting example is the work by Sullivan and Roberts.⁴⁰ The lack of an infrared absorption due to an $-\text{SO}_2\text{NH}-$ group lead Schwenker⁴¹ to conclude that the correct structure for sulfaguandinine was 5 and not the tautomeric structure 6. A ^{13}C NMR investigation⁴²



5



6

pointed to structure 6. However, the ^{15}N spectrum of sulfaguandinine shows three resonances at positions δ 212.3 ppm (singlet), δ 309.3 ppm (triplet), and δ 295.0 ppm (triplet). The intensity of the triplet at δ 295 ppm is twice that of the triplet at δ 309 ppm, strongly suggesting structure 5 with the chemical shift position of the two $-\text{NH}_2$ groups of the guanidine overlapping. X-ray study⁴³ shows structure 5 to also exist in the solid state.

^{15}N NMR has been used in the conformational analysis of amides⁴⁴ and lactams.⁴⁵ Williamson and Roberts⁴⁵ have studied lactams of varying ring size and have found no correlation between the chemical shift of the nitrogen and ring size (δ ^{15}N = 256.7 ± 3.1 ppm upfield from H^{15}NO_3). Large ring lactams, 10-membered or larger, are found in the trans conformation, while smaller ring lactams, 8-membered or smaller, are found in the cis conformation. The crossover point is the 9-membered lactam which showed a 2-3 ppm shift difference for the amide nitrogen in the cis and trans conformation, the trans conformation appearing at higher field.

G. L. Martin and coworkers⁴⁴ have found a linear correlation of the chemical shift for the amide nitrogen with the energy of activation (E_a) for rotation about the amide bond. After studying several amides with known activation energies, they proposed Eq. 3, which relates the $\delta^{15}\text{N}$ (relative to $^{15}\text{NO}_3^-$) to the E_a for rotation.

$$E_a (\pm 0.7 \text{ kcal/mol}^{-1}) = 80.0 + 0.217(\pm 0.015)\delta^{15}\text{N ppm} \quad (3)$$

Conclusion

Although there has been a rapid growth in ^{15}N NMR spectroscopy, the detection of this nucleus at the natural-abundance level will probably continue to be non-routine (acquisition transients 30,000 to 300,000). This will probably seriously impede its widespread use in the study of molecules of limited quantity, *i.e.*, large biological molecules. After the excitement associated with its novelty fades, ^{15}N NMR will most likely settle back to being a useful spectroscopic technique (*i.e.*, the work done on the porphyrins, Gramicidin S, protonation studies) for enriches samples in the hands of well-funded chemists (instrument costs > \$250,000).

BIBLIOGRAPHY

1. G. E. Hawkes, E. W. Randall, and C. H. Bradley, *Nature*, 257, 767 (1975).
2. "Nitrogen NMR", Witanoski, Ed., Plenum Press, New York, 1973.
3. R. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, 93, 3200 (1971).
4. D. Giannini, I. Armitage, H. Pearson, D. Grant, and J. D. Roberts, *J. Am. Chem. Soc.*, 97, 3416 (1975).
5. M. Witanoski, *Pure Appl. Chem.*, 37, 225 (1974).
6. G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972.
7. J. D. Roberts and R. L. Lichter, *J. Am. Chem. Soc.*, 94, 2495 (1972).
8. G. E. Hawkes, W. Litchman, and E. Randall, *J. Mag. Res.*, 19, 225 (1975).
9. C. S. Irving and A. Lapidot, *J. Am. Chem. Soc.*, 97, 5945 (1975).
10. G. C. Levy, C. Holloway, R. Rosanke, and J. Hewitt, *Org. Mag. Res.*, 8, 643 (1976).
11. R. E. Wasylshen and T. Schaeffer, *Can. J. Chem.*, 51, 3087 (1973).
12. T. Axenrod, P. Pregosin, M. Wieder, E. Becker, R. Bradley, and G. Milne, *J. Am. Chem. Soc.*, 93, 6536 (1971).
13. J. Schulmann, J. Ruggio, and T. Venanzi, *J. Am. Chem. Soc.*, 99, 2045 (1977).
14. J. P. Warren and J. D. Roberts, *J. Phys. Chem.*, 78, 2507 (1974).
15. S. Karplus and M. Karplus, *Proc. Nat. Acad. Sci. U.S.*, 69, 3204 (1972).
16. V. Bystrov, Yu. Gavrilov, and V. Solkan, *J. Mag. Res.*, 19, 123 (1975).
17. G. Binsch, J. Lambert, B. Roberts, and J. D. Roberts, *J. Am. Chem. Soc.*, 86, 5564 (1964).
18. G. A. Olah and A. M. White, *J. Am. Chem. Soc.*, 90, 6087 (1968).
19. J. D. Roberts, D. Gust, and R. Moon, *Proc. Nat. Acad. Sci. U.S.*, 72, 4696 (1975).
20. R. Cooper, R. Lichter, and J. D. Roberts, *J. Am. Chem. Soc.*, 95, 3724 (1973).

21. T. K. Leipert and J. Noggle, *J. Am. Chem. Soc.*, 97, 269 (1975).
22. T. Suzuki, T. Yamaguchi, and M. Imanari, *Tetrahedron Lett.*, 1809 (1974).
23. F. Blomberg, W. Maurer, and H. Rüterjans, *J. Am. Chem. Soc.*, 99, 8149 (1977).
24. F. Blomberg, W. Maurer, and H. Rüterjans, *Proc. Nat. Acad. Sci. U.S.*, 73, 1409 (1976).
25. T. Posner, V. Markowski, P. Loftus, and J. D. Roberts, *J. Chem. Soc., Chem. Commun.*, 769 (1975).
26. W. Horsley and H. Sternlicht, *J. Am. Chem. Soc.*, 90, 3738 (1968).
27. V. Markowski, G. Sullivan, and J. D. Roberts, *J. Am. Chem. Soc.*, 99, 714 (1977).
28. T. Nakajuna and A. Pullman, *J. Chim. Phys. Phys. Chim. Biol.*, 55, 793 (1958).
29. C. R. Dekker, *Ann. Rev. Biochem.*, 29, 453 (1960).
30. K. Shikata, T. Ueki, and T. Mitsui, *Acta Crystallogr. (B)*, 29, 31 (1973).
31. A. Cain, G. Sullivan, and J. D. Roberts, *J. Am. Chem. Soc.*, 99, 6423 (1977).
32. J. Fournier, E. Vincent, A. Chauvet, and A. Crevat, *Org. Mag. Res.*, 5, 573 (1973).
33. K. Kawano, Y. Ozaki, and Y. Kyogoku, *J. Chem. Soc., Chem. Commun.*, 226 (1977).
34. D. Gust and J. D. Roberts, *J. Am. Chem. Soc.*, 99, 3637 (1977).
35. C. Storm and Y. Teklu, *J. Am. Chem. Soc.*, 94, 1745 (1972).
36. R. Abraham, H. Pearson, K. Smith, P. Loftus, and J. D. Roberts, *Tetrahedron Lett.*, 1483 (1974).
37. R. Botto and J. D. Roberts, *J. Org. Chem.*, 42, 2247 (1977).
38. D. Dorman, J. Paschal, and K. Merkel, *J. Am. Chem. Soc.*, 98, 6885 (1976).
39. R. Lichter and D. Dorman, *J. Org. Chem.*, 41, 582 (1976).
40. G. Sullivan and J. D. Roberts, *J. Org. Chem.*, 42, 1095 (1977).
41. G. Schwenker, *Arch. Pharm.*, 295, 753 (1962).
42. C. Chang and H. Floss, *J. Med. Chem.*, 18, 505 (1975).
43. M. Alleaume, A. Gulko, F. Herbstein, M. Kapon, and R. Maroh, *Acta Crystallogr. (B)*, 32, 669 (1976).
44. G. Martin, J. Gouesnard, J. Dorie, C. Rabiller, and M. Martin, *J. Am. Chem. Soc.*, 99, 1381 (1977).
45. K. Williamson and J. D. Roberts, *J. Am. Chem. Soc.*, 98, 5082 (1976).

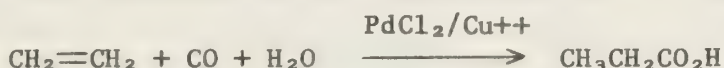
STEREOCHEMICAL ASPECTS OF PALLADIUM CATALYZED CARBONYLATIONS

Reported by Matt White

April 3, 1978

An increased interest in organopalladium chemistry has arisen in the past few years due partially to the observations that palladium complexes catalyze a number of organic transformations, that their reactions are regioselective, stereoselective, or stereospecific, and that the palladium catalysts are easy to regenerate.¹

Carbonylations. The carbonylation or the carbonyl insertion reaction is one in which carbon monoxide is added to an olefin or inserted into a σ carbon palladium bond. The carbonylation reaction has been observed with most transition metals. Many of the mechanistic details for palladium catalyzed carbonylations have not been worked out since



the problem of elucidation of reaction pathways for transition metals is complex and a plethora of products is produced. Kinetics provides information about the rate determining step, which in many cases is the least interesting, *i.e.*, π complex formation or carbon palladium σ bond formation. However, some good mechanistic work has been done especially with Co and Mn carbonyls since Co and Mn carbonyl and acyl compounds are more stable than their palladium analogues. Noack and Calderazzo's work on carbonylation of $\text{CH}_3\text{Mn}(\text{CO})_5$ showed that carbonyl insertion occurred *via* alkyl migration;² for palladium, reaction pathways are presently speculative.

The stereochemistry of palladium catalyzed carbonylation reactions has recently been investigated. Hines and Stille have shown by studies of the carbonylation of σ bonded methoxy adducts of dichloro(nonbornadiene)palladium(II), dichloro(1,5-octadiene)palladium(II), and dichloro-(endo-dicyclopentadiene)palladium(II) complexes that the carbonylation reaction proceeds with 100% retention of configuration at the carbon to which the metal was σ bonded.^{3,4} Since carbon monoxide has been shown to insert into carbon palladium σ bonds and the stereochemistry of the carbonylation reaction has been elucidated, the carbonyl insertion reaction has been used to examine the stereochemistry of the organic moiety of other organotransition metal reactions in which carbon palladium σ complexes are formed.^{5,6}

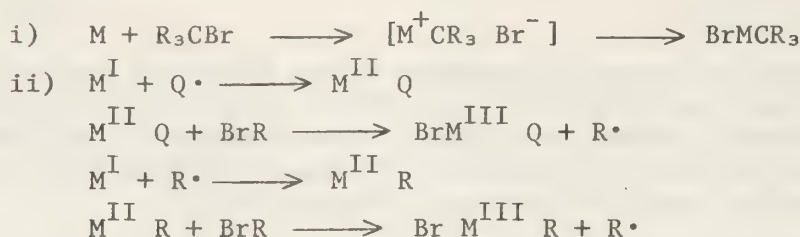
Oxidative Additions. An oxidative addition is a reaction in which an organic halide is added to a transition metal complex. This reaction provides a common synthetic pathway to organotransition metal complexes.⁷



R = alkyl, aryl, vinyl, allyl X = Cl, Br, I

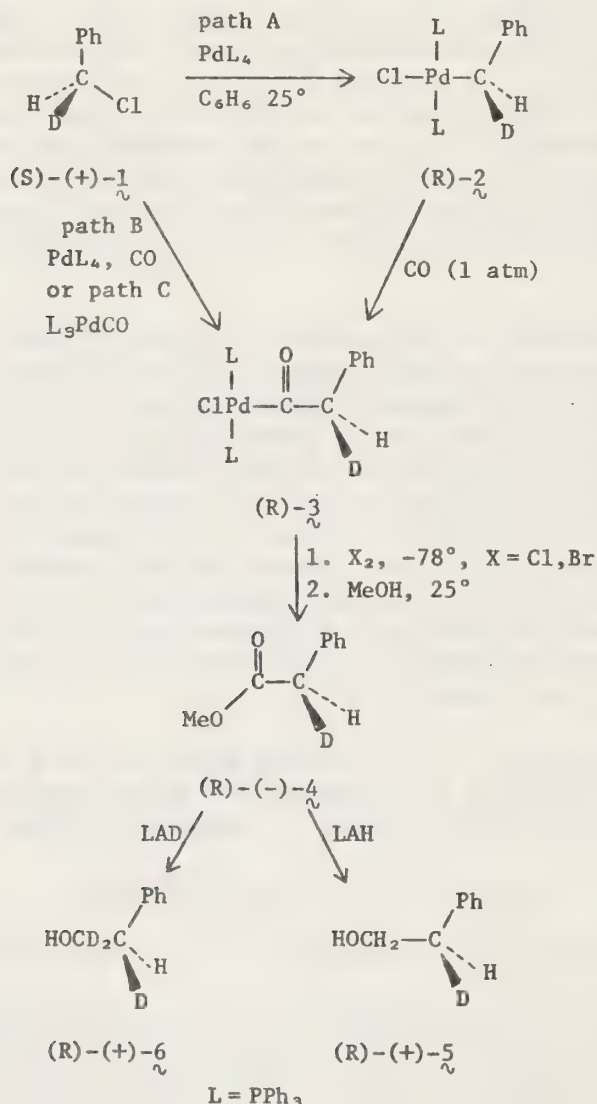
Investigations into the mechanism of oxidative additions is an active field. Two mechanistic pathways are currently under investigation: (i) a nucleophilic displacement by the palladium complex⁷ and (ii) homolytic cleavage followed by addition to the metal by radical intermediates.⁸ Oxidative additions have been shown to occur by either mechanism

(i) or (ii) depending upon the nature of the reactants and the conditions of the reaction.⁹⁻¹¹



Stille and coworkers have used the carbonylation reaction to examine the stereochemistry of oxidative additions in order to differentiate between processes (i) and (ii).¹² The chloride (S)-(+)-1 was converted to (R)-3 then freed as the methyl ester and reduced to the alcohol (Scheme I). With PdL_4 ($\text{L} = \text{PPh}_3$) as catalyst, path A,

Scheme I

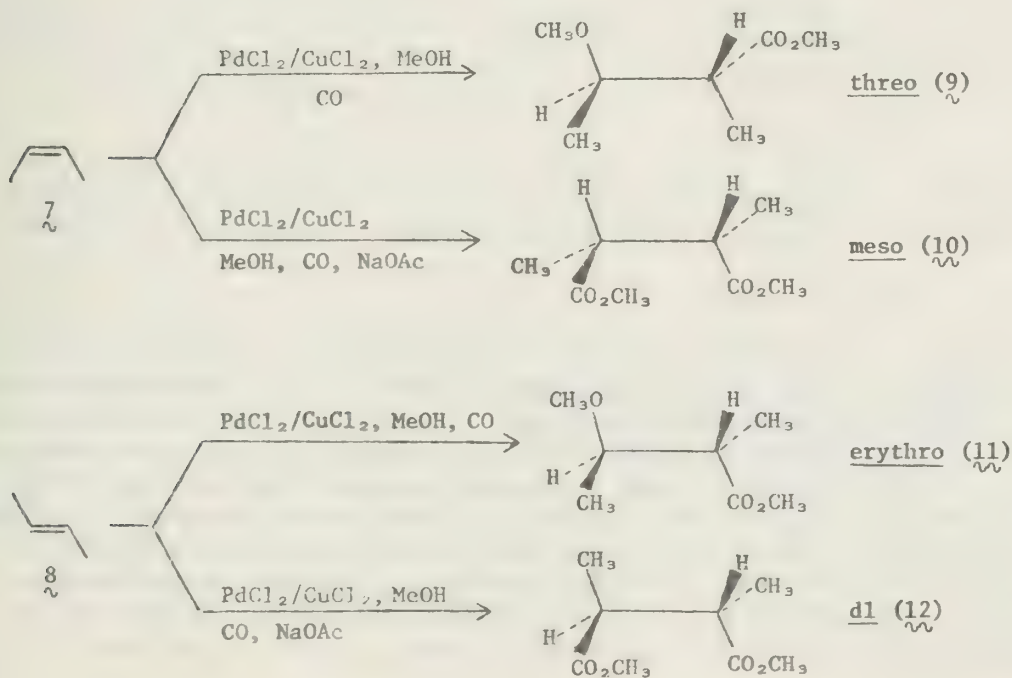


(R)-(-)-4 and (R)-(+)-5 were observed with R configurations as shown by specific rotations and ^1H NMR with $\text{Eu}(\text{dcm})_3$ (dcm = d,d-dicampholyl-methanto anion) as chiral shift reagent. Since carbonylation occurs with 100% retention, the oxidative addition must occur with inversion of configuration at carbon to which the metal was σ bonded. However, there was a definite loss of optical purity since the overall stereospecificity was 74%. When PdL_4 interacts directly with CO, path B, or with $\text{Pd}(\text{CO})\text{L}_3$, path C, (R)-(+)-5 was found to be formed with an overall stereospecificity of 100%. This indicated that oxidative addition occurred by inversion at the carbon to which the metal was σ bonded.

Stille and coworkers have found that during oxidative addition α -phenethyl bromide undergoes inversion of configuration at carbon with 90-95% enantiomeric excess.¹² This conclusion was reached by examining the methyl ester products from carbonylation by means of ^1H NMR using $\text{Eu}(\text{tfac})_3$ (tfac = 3-trifluoroacetyl-d-camphrato anion) as chiral shift reagent. The inversion of configuration about carbon is consistent with an $\text{S}_{\text{N}}2$ process. Further investigations on other palladium systems are needed to see if inversion of configuration at carbon is a general feature in oxidative additions to palladium complexes.

Stereochemical Aspects of the Carbonylation of Olefins. The addition of nucleophiles to olefins by means of metal complexes has been shown to be of synthetic utility.^{1,13} Stille and coworkers have allowed olefins in methanol at 3 atmospheres of CO at room temperature to react in the presence of $\text{PdCl}_2/\text{CuCl}_2$ to afford β -methoxy esters. When equimolar amounts of NaOAc based on olefin were added, the β -methoxy ester disappeared and 1,2-diester were obtained.¹⁴ The stereochemistry of this addition has been found to be dependent upon whether or not base was added to the reaction.¹⁵ When *cis*- and *trans*-2-butenes reacted with CO/ $\text{PdCl}_2/\text{CuCl}_2$ for 100 hours, *cis*-2-butene (7) yielded β -methoxy esters in a ratio of *threo* to *erythro* of 87:13; *trans*-2-butene (8) yielded β -methoxy ester in a *threo*/*erythro* ratio of 40:60 (Scheme II). Examina-

Scheme II

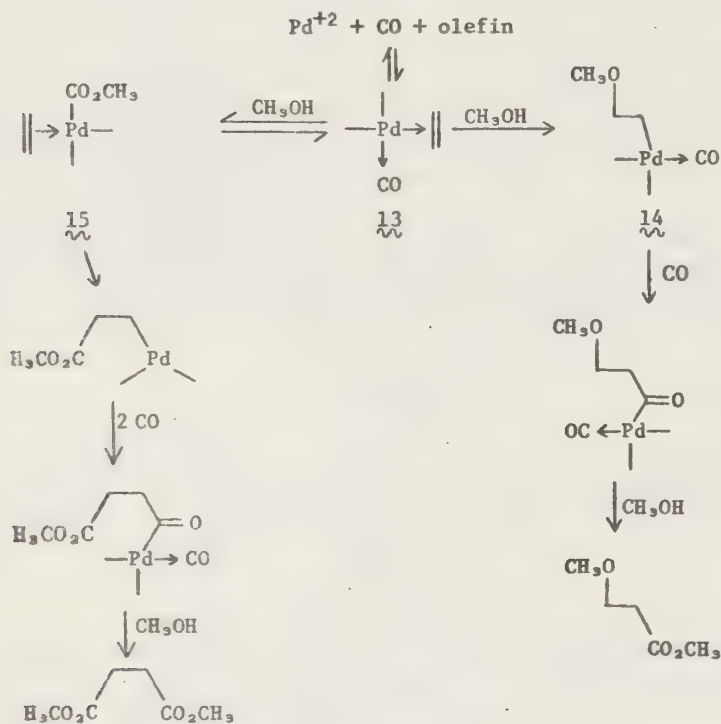


tion of unreacted olefin showed that cis-trans isomerization had occurred. After 2 and 8 hours of reaction, cis-2-butene (7) gave 100% threo product 9 while trans-2-butene (8) gave 100% erythro product 11 indicating a stereospecific trans addition to the olefin. When equimolar amounts of sodium acetate were added, β -methoxy ester formation was suppressed and succinic esters were formed. After 100 hours, trans-2-butene (8) formed dl-dimethylsuccinic ester (12) and cis-2-butene (7) formed the meso-dimethylsuccinic ester (10), indicating stereospecific cis-addition. No cis-trans isomerization of olefin was observed when base was added, suggesting the isomerization observed in the methanol cases was acid catalyzed.

A series of bases was examined to determine the influence of added base on the reaction. The salts of carboxylic acids increased the yields of diesters significantly, going from acetate to butyrate. Nitrogen bases gave poorer yields of diesters than the oxygen bases and did not eliminate the formation of the β -methoxy esters.

The mechanism in Scheme III was proposed to explain the elimination of the β -methoxy ester when base was added. This mechanism proposed the

Scheme III



initial formation of an olefin palladium π complex 13. In neutral conditions, alcohol is considered to attack the double bond, forming a methoxypalladium complex 14 which eventually forms the β -methoxy ester product. In the presence of base, methanol attacks the carbonyl of 13 forming carbomethoxypalladium complex 15. This scheme proposes that the rate of formation of 15 is increased when base is added, and base has been shown to increase the rate of formation of carbomethoxypalladium complexes.¹⁶ The mechanism speculates that complex 15 undergoes addition faster than methoxypalladation.

Various cyclic olefins were also studied. The major products isolated were trans- β -methoxy esters, cis-1,2-diester and cis-1,3-diester. The increased conversion to diester and strain energy correlated well with the exception of cyclooctene (Table 1). Hartley has suggested that cyclooctene palladium π complexes may be unstable due to steric effects.¹⁷ To test this proposal competition experiments between 1:1 molar ratios of cyclopentene and cyclooctene were performed. Cyclopentene was found to dominate the competition for the palladium catalyst. Instability of cyclooctene palladium π complexes could be the explanation for the anomalous position of cyclooctene.

Table 1.

Comparison of Strain Energy and the Carbonylation of Cyclic Olefins

<u>Olefin</u>	<u>% Diester^a</u>	<u>Strain Energy^b</u>
norbornene	82	27.2
cyclopentene	60	6.8
cycloheptene	58	6.7
cyclooctene	19	7.4
cyclohexene	5	2.5

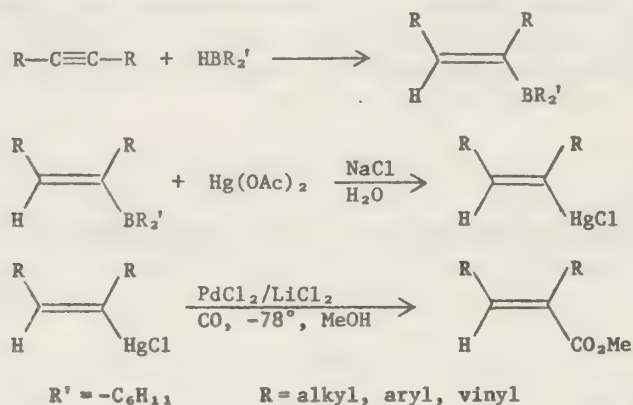
^aExcess of NaOAc present. ^bKcal/mole.

Primary olefins in the presence of CO, ROH (R = H, alkyl) and palladium phosphine complexes have been converted to saturated acids and esters.¹⁸ The ratio of straight to branched isomers was dependent upon the phosphine ligand employed. The monodentate ligands yielded primarily branched isomers and bidentate ligands yielded primarily linear isomers.¹⁹ Sugi and Bando in a series of experiments using bidentate ligands $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{P}(\text{Ph}_2)$ ($n = 1, 2, 3, 4, 5, 6, 10$) and styrene as substrate found in the $n = 3, 4, 5$ cases that the straight isomer, ethyl 3-phenylpropionate predominated.²⁰ In the $n = 1, 6, 10$ cases, the branched isomer ethyl 2-phenylpropionate dominated the mixture of esters. No reaction was observed in the $n = 2$ case. The authors also found with the monodentate ligands, PR_3 (R = phenyl, cyclohexyl, n-butyl) case, the variation in PR_3 group had little effect on the isomeric distribution; the branched isomer was favored selectively.

Similar trapping experiments have been used to examine σ carbon palladium intermediates in the Wacker process, the oxidation of ethylene to acetaldehyde in water.²¹ These experiments indicated that hydroxypalladation of the olefin is trans.

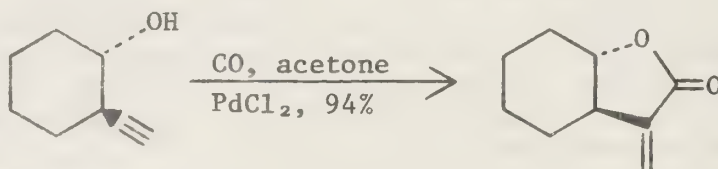
Stereochemistry of Carbonylation of Vinyl Halides. Heck has prepared vinyl palladium σ complexes and trapped them with CO to yield unsaturated acids and esters.²² The experiment with E and Z-3-iodo-3-hexenes gave a mixture of products, the E and Z vinyl esters and β,γ -unsaturated esters. The product with retention of configuration at the vinyl group was the major product formed. The mechanism of this procedure is an oxidative addition followed by carbonyl insertion. The processes involved in the loss of configuration about the double bond and β,γ -unsaturated ester formation are still unclear. Heck has also prepared unsaturated amides from benzyl, vinyl, and heterocyclic aromatic compounds under similar conditions in high yield and regioselectivity.²³

To eliminate the problem of isomerization about the double bond in the synthesis of vinyl esters and acids, Larock has prepared a stereospecific synthesis of α,β -unsaturated acids and esters from substituted acetylenes.²⁴ This procedure involved the use of vinylmercuric chloride intermediates which are readily available from acetylenes by means of vinyl borane derivatives.²⁵ High yields and stereospecificity were ob-

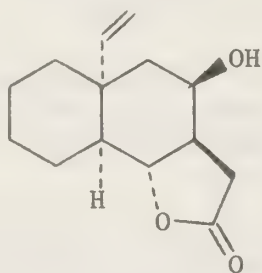


tained whether terminal or internal olefins were used. The stereoselectivity is derived from a Hg-Pd transmetalation reaction which has proven to go with retention at carbon followed by carbonylation.²⁵

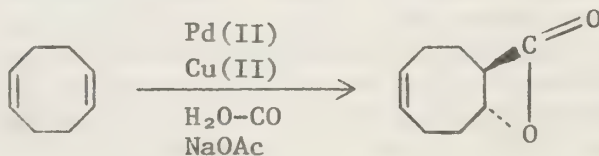
Stereospecific Synthesis of Lactones. Norton, Shenton, and Schwarz have converted stereochemically fixed cis, trans acetylenic alcohols to the corresponding cis, trans fused α -methylene lactones.²⁶ Chavdari,



Woo, Clark and Heathcock have used this procedure in the synthesis of the natural product bis- α -methylenelactone vernolepin.²⁷ Stille and co-



workers have synthesized trans β -lactones from olefins and bisolefins.²¹



BIBLIOGRAPHY

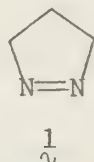
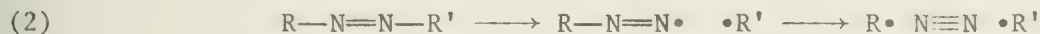
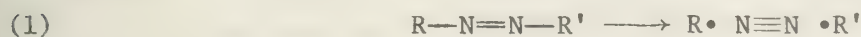
1. (a) P. M. Maitlis, "The Organic Chemistry of Palladium", Academic Press, New York, 1971; (b) "Organometallic Chemistry", Vol. 5, E. W. Abel and F. G. A. Stone, Eds., Burlington House, London, 1976.
2. (a) K. Noack and M. Calderazzo, *J. Organometal. Chem.*, 10, 101 (1967); (b) K. Noack and M. Calderazzo, *Inorg. Chem.*, 7, 345 (1968).
3. L. F. Hines and J. K. Stille, *J. Am. Chem. Soc.*, 94, 485 (1972).
4. J. K. Stille and L. F. Hines, *J. Am. Chem. Soc.*, 92, 1798 (1970).
5. P. K. Wong, K. S. Y. Lau, and J. K. Stille, *J. Am. Chem. Soc.*, 96, 5956 (1974).
6. J. K. Stille and K. S. Y. Lau, *J. Am. Chem. Soc.*, 98, 5841 (1976).
7. (a) S. D. Robinson, "Organometallic Chemistry", Vol. 5, E. W. Abel and F. G. A. Stone, Eds., Burlington House, London, 1976, p. 379; (b) J. A. Osborne, "Organotransition Metal Chemistry", Yoshio Ishii and Minoru Tsutsui, Eds., Plenum Press, New York, 1975, p. 65.
8. (a) P. B. Chock and J. Halpern, *J. Am. Chem. Soc.*, 88, 3511 (1966); (b) J. P. Collman and M. R. MacLaury, *J. Am. Chem. Soc.*, 96, 3019 (1974).
9. (a) A. V. Kramer and J. A. Labinger, *J. Am. Chem. Soc.*, 96, 7832 (1974); (b) D. Hopgood and R. A. Jenkins, *J. Am. Chem. Soc.*, 95, 4461 (1973).
10. F. R. Jensen, V. Madan, and D. H. Buchanan, *J. Am. Chem. Soc.*, 92, 1414 (1970).
11. J. S. Bradley, D. E. Connor, D. Dolphin, J. A. Labinger, and J. A. Osborne, *J. Am. Chem. Soc.*, 94, 4043 (1972).
12. K. S. Y. Lau, P. K. Wong, and J. K. Stille, *J. Am. Chem. Soc.*, 98, 5832 (1976).
13. P. M. Henry, *Accts. Chem. Res.*, 6, 16 (1973).
14. D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, 98, 1810 (1976).
15. D. E. James, L. F. Hines, and J. K. Stille, *J. Am. Chem. Soc.*, 98, 1806 (1976).
16. M. Hidai, M. Kokura, and Y. Uchida, *J. Organometal. Chem.*, 52, 431 (1973).
17. F. R. Hartley, *Chem. Rev.*, 73, 163 (1973).
18. (a) J. F. Knifton, *J. Org. Chem.*, 41, 2885 (1976); (b) K. Bittler, N. V. Kutepow, D. Newbauer, and H. Reis, *Angew. Chem.*, 80, 352 (1968).
19. (a) Y. Sugi, K. Bando, and S. Shin, *Chem. and Ind. London*, 75, 397 (1975); (b) G. Consiglio and M. Marchetti, *Chemia*, 30, 26 (1976).
20. Y. Sugi and K. Bando, *Chem. Lett.*, 19, 727 (1976).
21. J. K. Stille and R. Divakaruna, *J. Am. Chem. Soc.*, 100, 1303 (1978); (b) J. E. Backwall, B. Akermark, and M. C. Weis, *J. Chem. Soc., Chem. Commun.*, 264 (1977).
22. A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, 39, 3318 (1974).
23. A. Schoenberg and R. F. Heck, *J. Org. Chem.*, 39, 3327 (1974).
24. R. C. Larock, *J. Org. Chem.*, 40, 3237 (1974).
25. R. C. Larock and H. C. Brown, *J. Organometal. Chem.*, 36, 1 (1972).
26. J. R. Norton, K. E. Shenton, and J. Schwarz, *Tetrahedron Lett.*, 51 (1975).
27. C. J. Chavdari, Sam L. Woo, Robin D. Clark, and C. H. Heathcock, *Tetrahedron Lett.*, 1769 (1976).

THE EFFECTS OF UNSATURATION IN CYCLIC AZO COMPOUND DECOMPOSITION

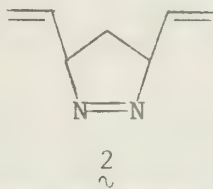
Reported by William F. Burgoyne

April 6, 1978

Azoalkanes, which have been of interest for over 40 years,^{1a} have provided convenient sources of alkyl radicals.^{1a-h} However, there still remains some controversy as to the means by which these compounds undergo thermal decomposition. Some authors have favored a concerted two-bond cleavage (Eq. 1), while others have provided evidence for one-bond cleavage (Eq. 2) and thus the formation of a diazenyl radical intermediate.^{1g} The cyclic analogues of azoalkanes have added further complexity to the event of nitrogen expulsion. Perhaps the most thoroughly studied types of cyclic azoalkanes are the 1-pyrazolines (1). Experimental evidence by various authors² has supported several mechanisms for the decomposition of alkyl substituted 1-pyrazolines under thermal and photochemical conditions. The intense investigation of these compounds has made them a topic for discussion and a subject of review.^{1f,3}



The introduction of unsaturation into cyclic azo compounds, either substituted α to nitrogen as in 3,5-divinyl-1-pyrazoline (2) or contained within the ring as with 1,2-diazacyclohexa-1,4-diene (3), has provided yet another dimension to the reactions of azo compounds and the postulated mechanisms for their decomposition. These two types of azo compounds form the basis of this review.



The reactions of 1-pyrazolines, having vinyl substituents α to nitrogen, have been of considerable interest in recent years.⁴⁻¹⁰ Schneider and coworkers^{5,7} demonstrated the first examples of a concerted cleavage of both carbon-nitrogen bonds in the decomposition reactions of cis- and trans-3,5-divinyl-1-pyrazolines (2c and 2t). The photochemical decomposition in solution and the gas phase thermolysis, 0°-60°, of 2c and 2t produced mixtures of trans-1,2-divinylcyclopropane (4) and 1,4-cycloheptadiene (5) in the proportions listed in Table I. In contrast to the decomposition products from 3,5-dialkyl-substituted 1-pyrazolines,³ both 2c and 2t have been shown to give similar yields of 3-membered-ring and 7-membered-ring products, in this case 4 and 5. With supportive evidence from kinetics provided by Crawford,^{6,10} the intermediate has been interpreted in terms of the formation of a highly resonance-stabilized diallylic 1,3-biradical (8) of extended lifetime which can undergo several rotations before ring closure can occur.⁴

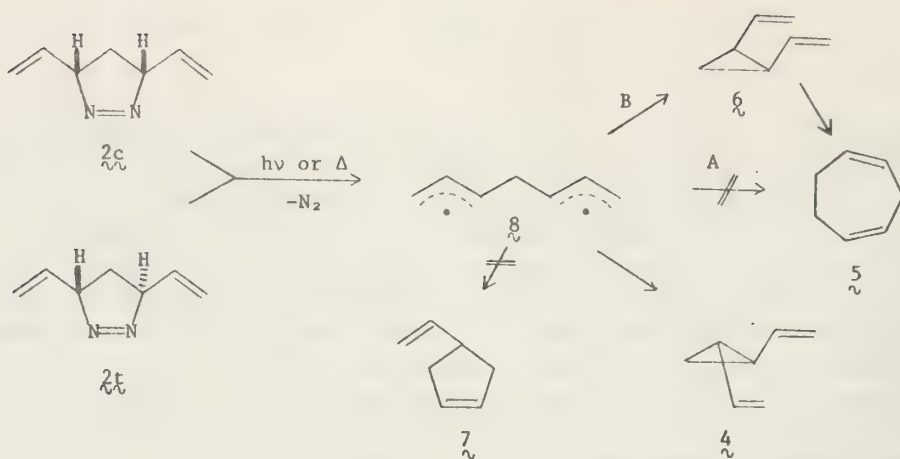


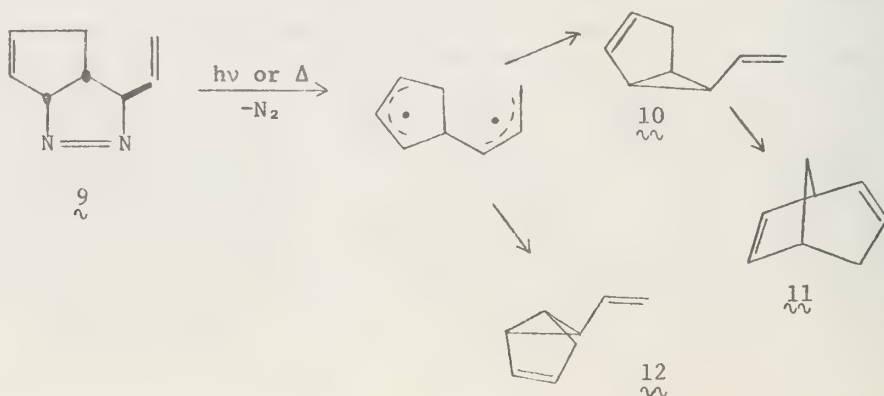
Table I⁷

	% Yield, thermal (0°-60°)		% Yield, photochemical		
	4	5	4	5	(P) ^a
2c	38	62	42	56	0-2
2t	37	63	56	42	0-2

^aTentatively assigned as 1,3,5-heptatriene.

The distinction between the direct ring closure of an isomer of **8** (Path A) or the result of cis-1,2-divinylcyclopropane (**6**) (Path B) in the formation of **5** has been resolved through the use of low temperature photolysis (-50°C) monitored by ¹H-NMR spectroscopy.^{7,11} These results, which indicate the formation of only **4** and **6** without the presence of 1,4-cycloheptadiene (**5**) or 4-vinylcyclopentene (**7**), have been rationalized by the predictable loss of resonance energy of **5** up to 12-14 kcal/mole from rotation if **5** and **7** were formed directly from **8**.¹² Based also on previous work,^{13a} compound **5** results from the photochemical and also probably from the thermal decomposition of **2c** and **2t** via Cope rearrangement of the initially formed compound **6**.

The bicyclo analog, exo-4-vinyl-2,3-diazabicyclo[3.3.0]octa-2,7-diene (**9**) has provided further evidence⁵ of the proposed mechanism in that compound **10** has been observed in low temperature photolysis and thermolysis in addition to the expected products **11** and **12**.^{13b}



When phenyl groups are present in place of 3,5-divinyl substitution, decomposition follows two possible paths,⁸ either one-bond cleavage and formation of a diazenyl biradical intermediate or the formation of a di-benzylic 1,3 biradical. The thermal and photochemical decompositions of the diphenyl-substituted compounds 13c and 13t are reported⁸ to yield only cis- and trans-1,2-diphenyl cyclopropane (14c and 14t) in the proportions indicated in Table II, while kinetics data suggested that each phenyl group contributes up to 8 kcal/mole toward the decrease in activation enthalpy.¹⁴

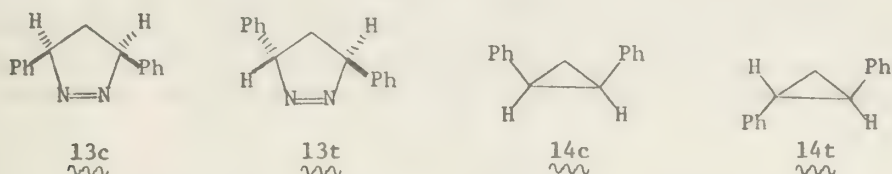
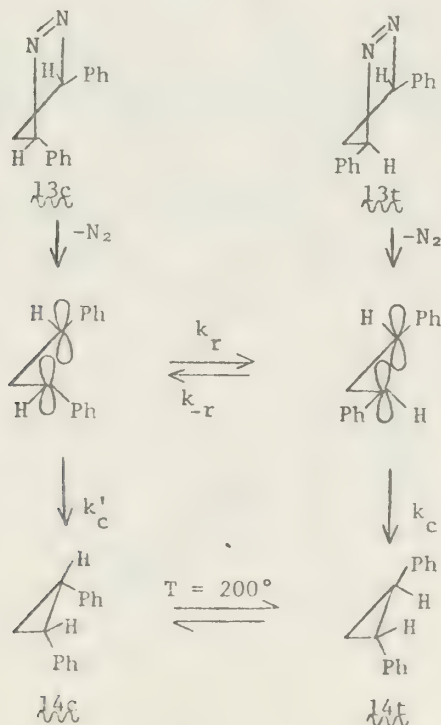


Table II⁸

	% Yield, thermal (40°-80°)		% Yield, photochemical	
	<u>14c</u>	<u>14t</u>	<u>14c</u>	<u>14t</u>
<u>13c</u>	45	55	51.5	48.5
<u>13t</u>	11	89	14.5	85.5

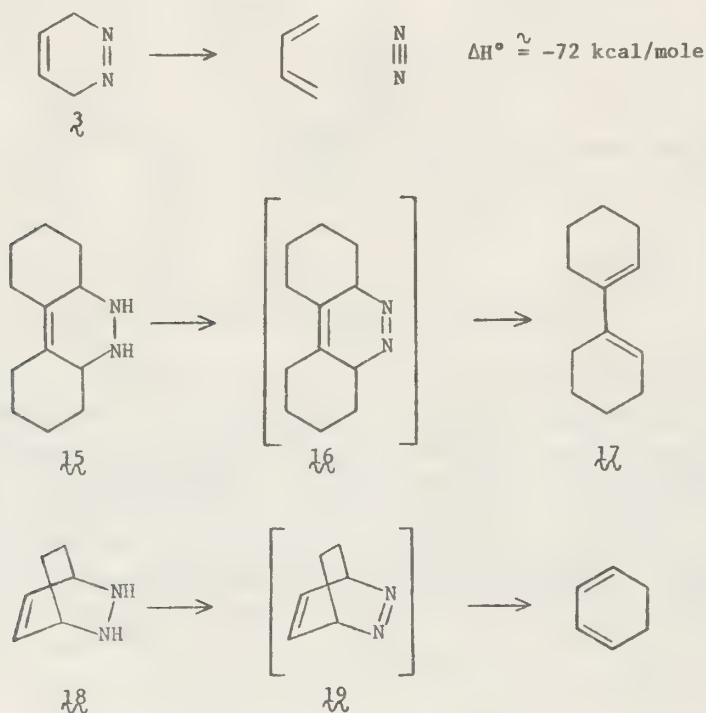
Since the product distribution cannot be rationalized by a "two-step," diazenyl radical mechanism, the mechanism that best describes the products proceeds by a nitrogen-free intermediate, as that shown in Scheme I. The product proportions result from competition between ring closure (k_c and k'_c) and the rotation isomerism (k_r and k_{-r}) of the intermediate. Steady state treatment of the product data has revealed k_r/k_c to be roughly five times larger than k_{-r}/k'_c .⁸ Observed temperature dependence on product selectivity

Scheme I

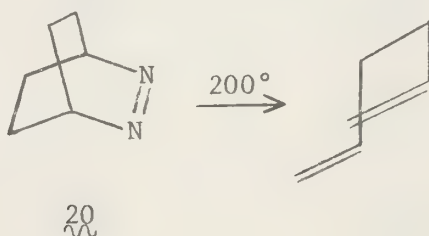


has been proposed as being a reflection of rotational isomerism competing favorably with the ring closure reaction. The intermediate biradical in Scheme I is thought also to be involved in the observed interconversion of 14c and 14t above 200°. Starting from either 14c or 14t, an identical thermodynamic equilibrium mixture ($K_{eq} \approx 10$) is obtained.⁸

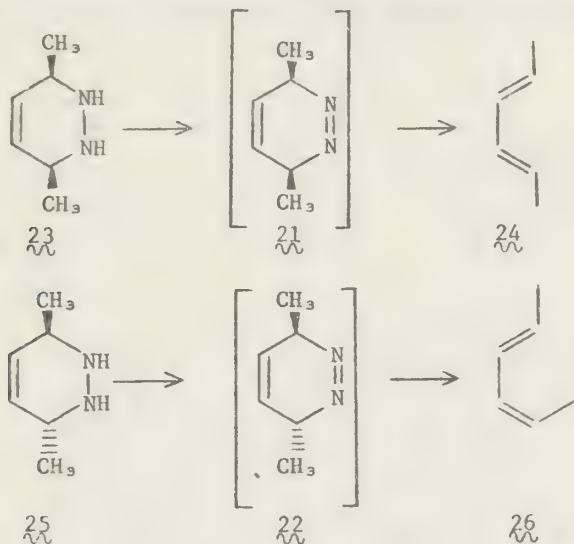
Cyclic analogues such as 1,2-diazacyclohexa-1,4-diene (3) are represented by a number of species which have been generated in situ but rarely isolated or observed. Their instability is a result of spontaneous nitrogen extrusion by way of a concerted cyclo reversion.¹⁵⁻²⁰ The exothermicity of 3 has been estimated to be ~ -72 kcal/mole based on decomposition of azomethane to ethane and nitrogen.¹⁵ Gillis and Beak¹⁶ report that diene 17 is the only observed product of the oxidation of the olefinic hydrazo compound 15,



presumably through an intermediate such as 16. Similarly, 2,3-diazabicyclo-[2.2.2]octa-2,5-diene (19), presumably formed from the oxidation of hydrazo compound 18, decomposes to cyclohexa-1,3-diene and nitrogen even at temperatures of -78° .¹⁷ Comparatively, the dihydro compound 20 is a very stable compound that decomposes only at $\sim 200^\circ\text{C}$, yielding 1,5-hexadiene.¹⁸ The mechanism for decomposition of 20 is not a symmetry-allowed concerted process, but has been suggested to proceed by a multistep reaction sequence.^{18c}

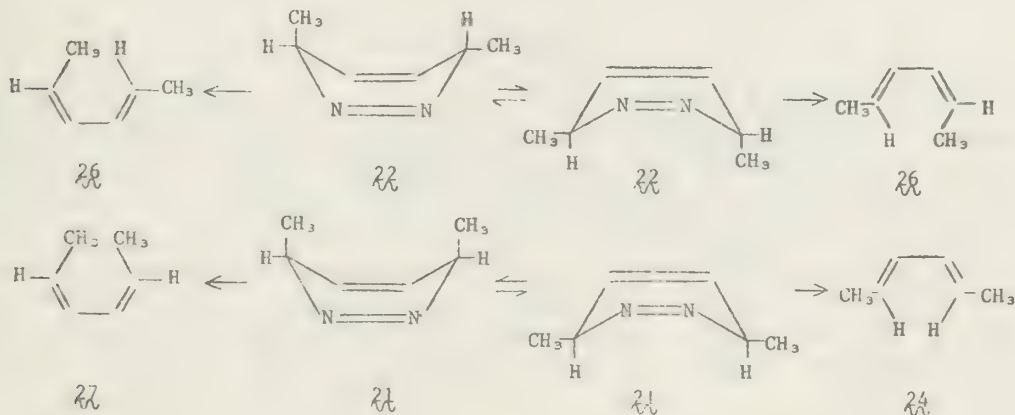


Decomposition of the stereochemically labeled 1,2-diazacyclohexa-1,4-dienes (21 and 22), according to Berson,²¹ has provided evidence not only for reaction concertedness but also for stereospecificity which is deemed necessary by orbital symmetry conservation.²² Oxidation of cis-hydrazo compound 23 by yellow mercuric oxide or manganese dioxide brought about quantitative nitrogen evolution with trans, trans-hexa-2,4-diene (24) as the only volatile product.²¹ Similar oxidation of 25 resulted in only cis, trans-hexa-2,4-diene (26). The observed retro-Diels-Alder reaction of 21 and 22 is presumed to evolve with the leaving dienophile

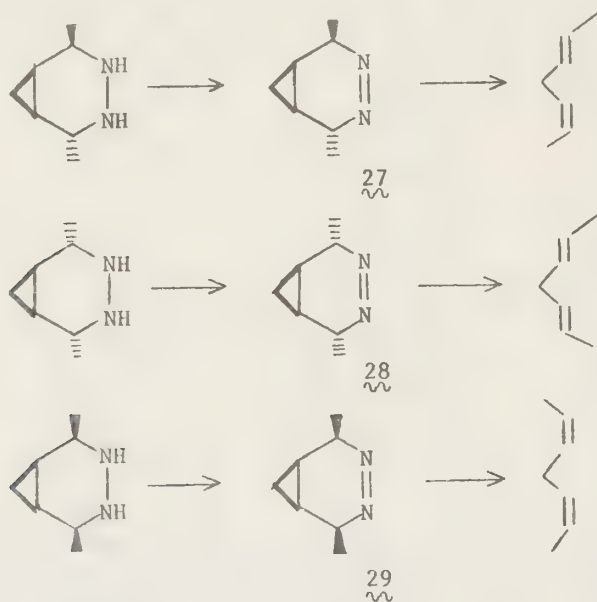


(N₂) departing by a pathway that is strictly cis in both cases. The exclusive product formation in these reactions has been clearly rationalized by the Woodward-Hoffmann approach.^{22a} Such interpretation provides for two allowed processes which can proceed by disrotation. As illustrated in Scheme II, trans-azo compound 22 can only lead to cis, trans-hexa-2,4-diene (26) by disrotation. However, cis, cis- or trans, trans-hexa-2,4-diene can result in theory from compounds 21. The exclusive formation of the trans, trans product (24) and the strict avoidance of product 27 is suggested to result from severe steric repulsions between the methyl groups, which must assume the unfavorable flagpole type configuration en route to 27.²¹

Scheme II

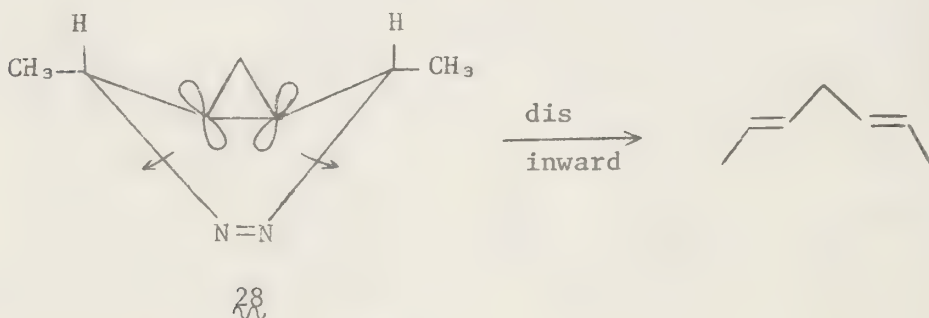


Replacement of the carbon-carbon double bond with a cyclopropane fused ring has given rise to a homo-Diels-Alder cycloreversion. Azo compounds 27, 28, and 29, obtained by oxidation from the corresponding dihydroazo compounds, have been observed by both NMR and UV spectroscopy at temperatures below -70° , but are found to decompose gradually at -10° ($t_{1/2}=30$ min) and rapidly at room temperature to give nitrogen and hepta-2,5-dienes.^{15,21,23} The formation of the dienes was reported to be highly stereospecific with the trans-, anti-cis- and syn-cis-azo compounds (27, 28 and 29) giving respectively cis-, trans-, trans-, trans-, and cis-, cis-hepta-2,5-diene, each in $>99.5\%$ isomeric purity. Hypothetical ring closure products from these azo compounds, which were found to be stable under conditions of the decomposition, were not observed.¹⁵



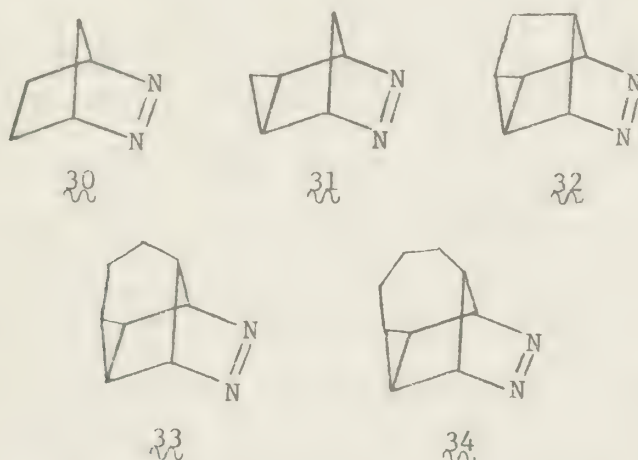
The stereospecificities in the cycloreversion of 27, 28, and 29 were shown to have a strong preference for inward-disrotation with nitrogen departing anti to the cyclopropane ring. These findings were rationalized as the result of the p orbitals (as in the Walsh model of cyclopropane²⁴) being almost parallel to the breaking carbon-nitrogen bonds.¹⁵ Such favorable overlap of orbitals provides for a concerted mechanism as shown in Scheme III.

Scheme III



The cyclobutane analogues of 27, 28 and 29 are reported³⁰ to decompose much more slowly than the cyclopropane case (31, 32 and 33), requiring a temperature of 200°C. This observation is explained in terms of the decreased "bent bond" character in the backbone bond of the cyclobutane analogues.³¹ However, the reactions are completely stereospecific, giving the corresponding octa-2,6-dienes with no observed ring closure products.

Kinetic studies conducted by Allred²⁵⁻³⁰ have provided further insight in the participation of the cyclopropane ring through a comparison of reactivities resulting from variations of the dihedral angle between the cyclopropane ring and the diazacyclohexane ring. Compound 32 was shown to be 10^7 - 10^{10} times less reactive than the structurally similar 31, 33 and 34.²⁵ Based on the similarity in reactivity between 30 and 32,



it was suggested that the decomposition of 32 proceeds by a diradical pathway²⁷ whereas the similarities in activation energies and entropies of 33 and 34 to those of 31 indicated a concerted process involving transition states as previously described. The rationalization for the differences in reactivity was based on the differences in strain in the transition state along with variation in the degree of p orbital overlap from the cyclopropane ring.

Studies relating the rates of reaction between endo- and exo-fused cyclopropane and cyclobutane have shown the presence of the exo-cyclopropane ring does not facilitate the fragmentation process as does analogous endo compounds.^{26,31} These studies further demonstrate the strict requirements of orbital orientation for concerted cycloreversion.

BIBLIOGRAPHY

1. (a) H. C. Ramsperger, J. Am. Chem. Soc., 51, 2134 (1929); (b) P. S. Engel and D. J. Bishop, *ibid.*, 97, 6754 (1975); (c) R. A. Johnson and S. Seltzer, *ibid.*, 95, 938 (1973); (d) A. Tsolis, S. G. Mylonakis, M. T. Nieh, and S. Seltzer, *ibid.*, 94, 829 (1972); (e) R. C. Neuman, Acc. Chem. Res., 5, 381 (1972); (f) for an excellent review of azoalkane decomposition, see O. P. Strausz, J. W. Lown, and H. E. Gunning, Compr. Chem. Kinet., 5, 566 (1972); (g) N. A. Porter and L. U. Marnett, J. Am. Chem. Soc., 95, 4361 (1973) and references cited therein; (h) A. F. Hegarty, Chem. Hydrazo, Azo, Azoxy Groups, 2, 643 (1975).

2. (a) R. J. Crawford and D. M. Cameron, *Can. J. Chem.*, 45, 691 (1967); (b) D. E. McGreer, R. S. McDaniel, and M. G. Vinje, *ibid.*, 43, 1389 (1965); (c) W. R. Roth and M. Martin, *Justus Liebigs Ann. Chem.*, 702, 1 (1967); (d) E. L. Allred and R. L. Smith, *J. Am. Chem. Soc.*, 89, 7133 (1967); (e) D. F. Eaton, R. G. Bergman, and G. S. Hammond, *ibid.*, 94, 1351 (1972); (f) D. H. White, P. B. Condict, and R. G. Bergman, *ibid.*, 94, 1348 (1972).
3. S. Braslavsky and J. Heicklen, *Chem. Rev.*, 77, 473 (1977), and references cited therein.
4. M. Schneider and I. Merz, *Tetrahedron Lett.*, 1995 (1974).
5. M. Schneider and G. Mössinger, *ibid.*, 3081 (1974).
6. R. J. Crawford and M. Ohno, *Can. J. Chem.*, 52, 3134 (1974).
7. (a) M. Schneider, *Angew. Chem.*, 87, 717 (1975); (b) M. Schneider, *Angew. Chem., Int. Ed. Engl.*, 14, 707 (1975).
8. M. Schneider and H. Strohäcker, *Tetrahedron*, 32, 619 (1976).
9. (a) R. J. Crawford and D. M. Cameron, *Can. J. Chem.*, 45, 691 (1967); (b) R. J. Crawford and K. Takagi, *J. Am. Chem. Soc.*, 94, 7406 (1972).
10. R. C. Newman, Jr. and E. W. Ertley, *ibid.*, 97, 3130 (1975), and references cited therein.
11. M. Schneider and J. Rebell, *J. Chem. Soc., Chem. Commun.*, 283 (1975).
12. (a) W. U. E. Doering and G. H. Beasley, *Tetrahedron*, 29, 2231 (1973); (b) W. R. Roth, G. Ruf, and P. W. Ford, *Chem. Ber.*, 107, 48 (1974).
13. (a) J. M. Brown, B. T. Golding, and J. J. Stofko, *J. Chem. Soc., Chem. Commun.*, 319 (1973); (b) J. M. Brown, *ibid.*, 226 (1965).
14. (a) J. C. Martin and J. W. Timberlake, *J. Am. Chem. Soc.*, 92, 978 (1970); (b) J. W. Timberlake and B. K. Bandlish, *Tetrahedron Lett.*, 1393 (1971).
15. J. A. Berson, S. S. Olin, E. W. Petrillo, Jr., and P. Bickart, *Tetrahedron*, 30, 1639 (1974).
16. B. T. Gillis and P. E. Beak, *J. Org. Chem.*, 28, 3177 (1963).
17. (a) R. Askani, *Chem. Ber.*, 98, 2551 (1965); (b) N. Rieber, J. Alberts, J. A. Lipsky, and D. M. Lemal, *J. Am. Chem. Soc.*, 91, 5668 (1969).
18. (a) S. G. Cohen and R. Zand, *J. Am. Chem. Soc.*, 84, 586 (1962); (b) M. Martin and W. R. Roth, *Chem. Ber.*, 102, 811 (1969); (c) W. R. Roth and M. Martin, *Tetrahedron Lett.*, 3865 (1967).
19. R. Askani, *Chem. Ber.*, 102, 3304 (1969).
20. C. R. Flynn and J. Michl, *J. Am. Chem. Soc.*, 95, 5802 (1973).
21. J. A. Berson and S. S. Olin, *ibid.*, 91, 777 (1969), and references cited therein.
22. (a) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N. Y., 1970, p. 101ff; (b) R. Hoffmann and R. B. Woodward, *Acc. Chem. Res.*, 1, 15 (1968).
23. J. A. Berson and S. S. Olin, *J. Am. Chem. Soc.*, 92, 1086 (1970).
24. A. D. Walsh, *Trans. Faraday Soc.*, 45, 179 (1949).
25. E. L. Allred and A. L. Johnson, *J. Am. Chem. Soc.*, 1300 (1971).
26. E. L. Allred and K. J. Voorhees, *ibid.*, 620 (1973).
27. E. L. Allred, J. C. Hinshaw, and A. L. Johnson, *ibid.*, 91, 3383 (1969).
28. E. L. Allred and J. C. Hinshaw, *Tetrahedron Lett.*, 387 (1972).
29. E. L. Allred and J. C. Hinshaw, *Chem. Commun.*, 1021 (1969).
30. (a) B. M. Trost, R. M. Covey, P. H. Scudder, and H. B. Neubold, *J. Am. Chem. Soc.*, 95, 7813 (1973); (b) H. Schmidt, A. Schweig, B. M. Trost, H. B. Neubold, and P. H. Scudder, *ibid.*, 96, 622 (1974); (c)

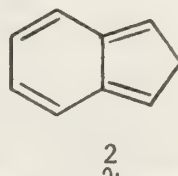
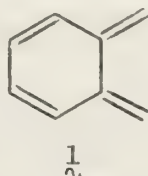
- H. E. Zimmerman, R. J. Boettcher, N. E. Buehler, G. E. Keck, and M. G. Steinmetz, ibid., 98, 7680 (1976); (d) R. J. Bold, J. C. G. Bünzli, and J. P. Snyder, ibid., 98, 2398 (1976); (e) H. Olsen and J. P. Snyder, ibid., 99, 1524 (1977).
31. (a) J. A. Berson, E. W. Petrillo, Jr., and P. Bickart, ibid., 96, 636 (1974); (b) C. A. Coulson and T. H. Goodwin, J. Chem. Soc., 2851 (1962); (c) C. A. Coulson and T. H. Goodwin, ibid., 3161 (1963); (d) L. A. Paquette and M. J. Epstein, J. Am. Chem. Soc., 95, 6717 (1973).

o-XYLYLENE COMPOUNDS

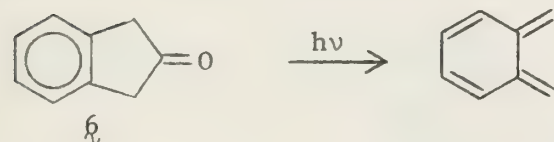
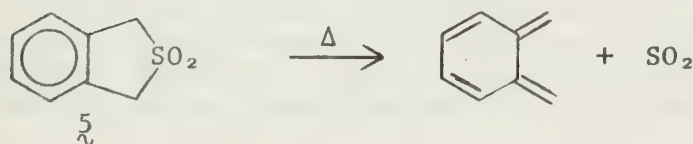
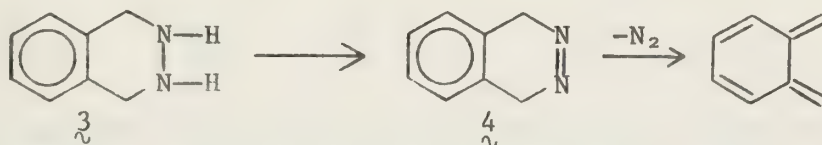
Reported by Jimmie P. Smith

April 10, 1978

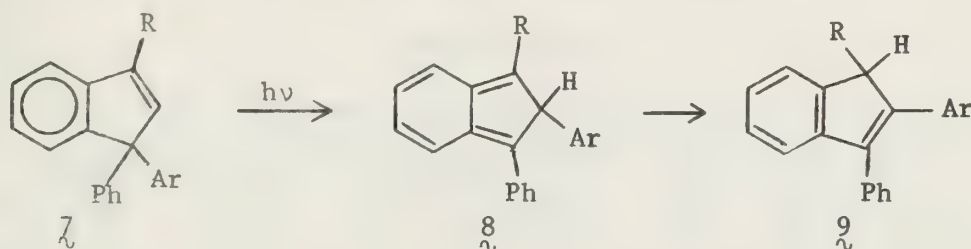
The o-xylylene system $\overset{1}{\sim}$ and the related isoindene $\overset{2}{\sim}$ have aroused much theoretical^{1,2} and experimental³⁻⁸ interest and have been detected by matrix isolation and flash photolysis.⁹ Until recently, only substituted o-xylylenes of differing stabilities have been observed, including a



stable metal complex¹⁰ of $\overset{1}{\sim}$, but evidence for $\overset{1}{\sim}$ had been indirect, based on trapping and self-trapping reactions. Some of the reactions which are believed to involve $\overset{1}{\sim}$ as a reactive intermediate are the oxidation of 1,2,3,4-tetrahydrophthalazine ($\overset{3}{\sim}$) at 0°, presumably proceeding via 1,4-dihydrophthalazine ($\overset{4}{\sim}$) and spontaneous elimination of N₂ at this temperature, and the thermal decomposition of 1,3-dihydroisethionaphthene 2,2-dioxide ($\overset{5}{\sim}$), as well as ultraviolet irradiation of 2-indanone ($\overset{6}{\sim}$).

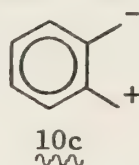
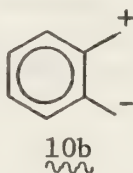
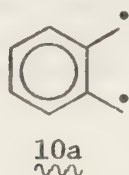


Isoindene derivatives have been invoked as intermediates in the photo-rearrangement of 1,1-diaryllindenenes. Thus, the rearrangement of $\overset{7}{\sim}$ to give $\overset{9}{\sim}$ has been proposed to proceed through the isoindene $\overset{8}{\sim}$.

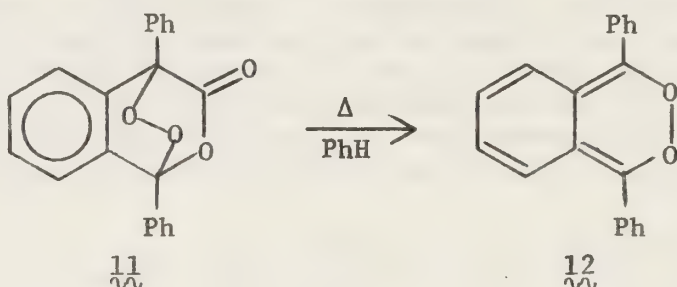


Theoretical studies^{1,2d} on the nature of the electronic structure of $\overset{1}{\sim}$ have been verified by the isolation of compound $\overset{1}{\sim}$ using the technique of matrix isolation.¹ The studies permit several conclusions to be made:

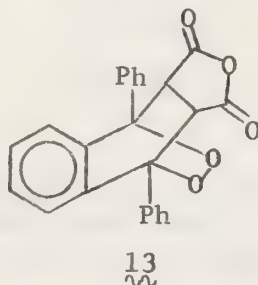
(1) the ground state of *o*-xylylene is a singlet, S_0 ; (2) S_0 and S_1 are planar; (3) S_2 , a partially doubly excited state, is approximately degenerate with S_1 ; (4) there is biradical character because of the degeneracy of the S_1 and S_2 states. The importance of structures 10a - 10c in various electronic states is as yet unknown.



In a preliminary communication¹¹ we have reported evidence for an *o*-xylylene peroxide, the first report of such a class of compounds. The peroxide 12 is believed to be formed upon decomposition of endoperoxide 11 in refluxing benzene. Evidence that supports the formation of 12 is



obtained from trapping experiments. When maleic anhydride was added to the benzene solution, a compound identified as 13 was isolated; therefore, a Diels-Alder reaction of the xylylene peroxide 12 with maleic anhydride is consistent with the formation of 13. Compounds with the *o*-xylylene moiety have been characterized in the absence of oxygen under mild conditions.¹² The absorption spectra and chemistry are similar to those which were found for the intermediate in the decomposition of 11.



BIBLIOGRAPHY

1. C. R. Flynn and J. Michl, *J. Am. Chem. Soc.*, **96**, 3280 (1974).
2. (a) J. D. Roberts, A. Sheitwieser, Jr., and C. M. Regan, *J. Am. Chem. Soc.*, **74**, 4579 (1952); (b) J. Kouteck and V. Bonacic-Koutecky, *Chem. Phys. Lett.*, **15**, 558 (1972); (c) N. C. Baird, *J. Am. Chem. Soc.*, **94**, 4941 (1972); (d) E. Migirdicyan and J. Baudet, *J. Am. Chem. Soc.*, **97**, 7400 (1975).
3. M. P. Cava and A. A. Deana, *J. Am. Chem. Soc.*, **81**, 4266 (1959).
4. N. C. Yang and C. Rivas, *J. Am. Chem. Soc.*, **83**, 2213 (1961).
5. N. S. Isaacs, *Can. J. Chem.*, **44**, 415 (1966).

6. K. H. Grellmann, J. Palmourski, and G. Quinkert, *Angew. Chem., Int. Ed. Engl.*, 10, 196 (1971).
7. R. D. Miller, J. Kolc, and J. Michl, *J. Am. Chem. Soc.*, 98, 8510 (1976).
8. K. de Fonseca, C. Manning, J. J. McCullough, and A. J. Yarwood, *J. Am. Chem. Soc.*, 99, 8257 (1977).
9. G. Porter and M. F. Tchir, *Chem. Commun.*, 1372 (1970).
10. W. R. Roth and J. D. Meier, *Tetrahedron Lett.*, 2053 (1967).
11. J. P. Smith and G. B. Schuster, *J. Am. Chem. Soc.*, in press.
12. (a) K. L. Tseng and J. Michl, *J. Am. Chem. Soc.*, 99, 4840 (1977); (b) W. R. Dolbier, Jr., K. Matsui, J. Michl, and D. V. Horak, *J. Am. Chem. Soc.*, 99, 3876 (1977); (c) E. Chacko, J. Bornstein, and D. J. Sardella, *Tetrahedron Lett.*, 1095 (1977); (d) D. S. Weiss, *J. Am. Chem. Soc.*, 97, 2250 (1975).

IODOTRIMETHYLSILANE: A VERSATILE ELECTROPHILIC REAGENT

Reported by Kenneth P. Moder

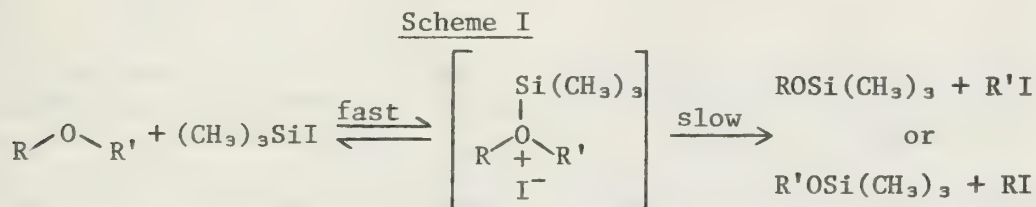
April 13, 1978

The challenge to many synthetic chemists in a rapidly developing field is to find novel synthetic reagents that perform under mild conditions. One such reagent is iodotrimethylsilane, a versatile electrophilic reagent, which has been used to cleave ethers and esters, convert alcohols to iodides, reduce sulfoxides, and convert ketals to ketones. Unlike the other halide derivatives, iodotrimethylsilane exhibits unique or facile chemical reactivity. Spectral data provide some insight into the anomalous reactivity of iodotrimethylsilane.

The use of alkyl ethers as alcohol protecting groups has found extensive use in organic chemistry. Certain functions such as *tert*-butyl, triphenyl-methyl (trityl), and benzyl can be readily removed under relatively mild conditions. However, the simplest alkyl ether, methyl, due to its stability, has found use only as a phenolic protecting group. Much effort has been devoted to finding methods to cleave methyl ethers.¹ The standard arsenal available for ether cleavage includes the following: strong nucleophiles,² Grignard reagents,³ phosphide compounds,⁴ Lewis acids,⁵ HI,^{1b,6} alkali metals,⁷ and aluminum hydrides.⁸ Cleavages of aliphatic methyl ethers with HI generated *in situ*, acetic anhydride-Lewis acid media, and boron compounds share the problem of not being clean and efficient, and they often result in mixtures of dealkylated products.

Treatment of ethers with iodotrimethylsilane⁹ results in clean C-O bond cleavage without producing mixtures of dealkylated products. It is possible to effect selective ether cleavage due to the differences in ether reactivities. The order of reactivity is trityl, benzyl, *t*-butyl \gg methyl, ethyl, *i*-propyl, cyclohexyl $>$ aryl. Since aryl-alkyl ethers react more sluggishly than do dialkyl ethers, one is able to cleave dialkyl ethers selectively under conditions which result in only minimal aryl-alkyl ether cleavage. Another important feature is that aryl-alkyl ethers react to afford only the phenol.

Jung^{9d} has proposed a mechanism for the cleavage of ethers by iodotrimethylsilane (Scheme I). The formation of a positively charged intermediate is supported by the fact that electron donor substituents on the



aromatic nucleus accelerate cleavage. Electron withdrawing substituents retard cleavage. Ortho substituents on the aryloxy group depress the rate. Finally, increases in the alkyl chain length also decrease the reaction rate.

Saturated cyclic ethers are also cleaved by iodotrimethylsilane. Reactions of TMSX compounds with THF and THP demonstrate the differences in reactivity of the different halogen derivatives. These reactions show clearly that the iodo derivative is more reactive and gives cleaner reactions.

Nonsaponificative hydrolysis of esters to their corresponding carboxylic acids is usually carried out by using strong nucleophiles,^{1b,10} fused nucleophilic salts,¹¹ boron reagents,¹² nitrosonium hexafluorophosphate,¹³ aluminum reagents,^{8,14} dipolar micelles,¹⁵ as well as intramolecular nucleophilic attack on modified esters.¹⁶ Some of these procedures require the use of strong nucleophiles at elevated temperatures. Other methods are not general.

While Lutsenko¹⁷ was the first to use iodotrimethylsilane on esters, Olah^{9f,g;18b} and Jung^{18a} have shown that iodotrimethylsilane, at moderate temperatures, can achieve clean ester hydrolysis under neutral conditions. The dealkylation of esters can be quantitative. Another advantage of ester hydrolysis with iodotrimethylsilane is the compatibility of the reagent with various functional groups. Ester hydrolysis is possible in the presence of isolated double bonds, ketones, aromatic ethers, furan, thioethers, amines, and amides. However, iodotrimethylsilane readily attacks dialkyl ethers, alcohols, and hydrolyzes some ketals to ketones in high yields. Ester hydrolysis is selective, providing care is exercised in selection of ester derivatives. Results show that *t*-butyl and benzyl esters, which are rapidly hydrolyzed at 25°C, can be selectively hydrolyzed in the presence of methyl, ethyl, and isopropyl esters. The latter esters are readily dealkylated at 50°C. No difference in selectivity is seen among methyl, ethyl, and isopropyl esters at 50°C (Table 1). Jung has

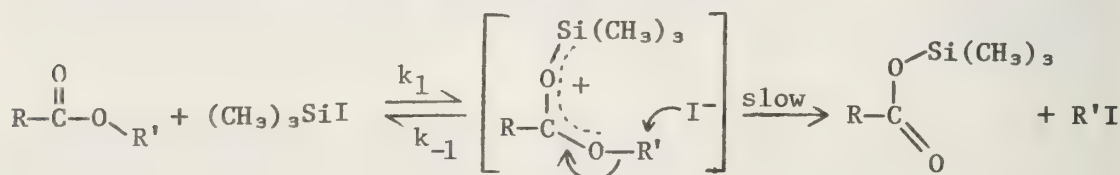
Table 1. Hydrolysis of Esters with Iodotrimethylsilane

R	R'	Method ^a	Time, h	Temp, °C	Yield, %
Ph	Me	A	24	130	100
Ph	Me	B	3	145	60
Ph	Me	C	2	100	80
Ph	Me	D	2	110	95
Ph	Me	E	35	50	85
Ph	PhCH ₂	B	3	reflux	72
Ph	PhCH ₂	C	2	100	86
Ph	PhCH ₂	D	2	110	92
Ph	PhCH ₂	F	0.5	25	0
Ph	PhCH ₂	E	1.5	25	100
Ph	Me	E	35	50	85
Ph	Et	E	48	50	100
Ph	<i>i</i> Pr	E	23	50	100
Ph	<i>i</i> Bu	E	0.5	25	90

^aA) LiI, NaCN/DMF; B) KSCN/DMF; C) TMSI; D) PhMe₃Si/I₂; E) TMSI/CCl₄; F) PhSNa/DMF

proposed the following mechanism for the iodotrimethylsilane hydrolysis of esters (Scheme II).

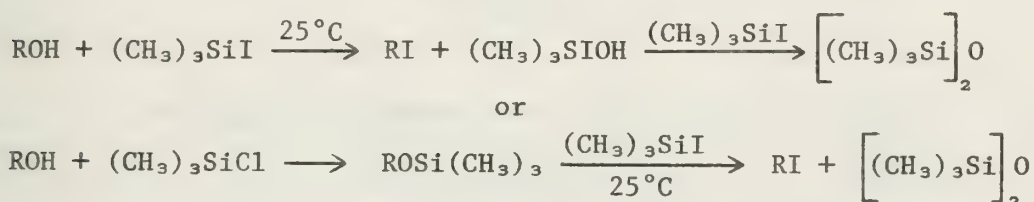
Scheme II



An interesting consequence of prolonged treatment of esters with iodotrimethylsilane is that the silyl ester first formed can react with more iodotrimethylsilane to form acid iodides. Synthesis of iodides from alcohols is an important and often necessary conversion. The standard methods of preparation have been a) the reaction of the alcohol with red phosphorus and iodine,¹⁹ and b) the reaction of the alcohol with HI generated in situ by the action of acid on iodine.^{6,20} More recent methods involve the use of phosphonates or phosphates,²¹ boron derivatives,²² or the modification of the hydroxyl to a better leaving group followed by iodide displacement.²³

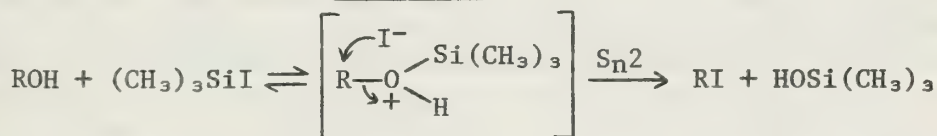
Ruhlmann^{24a} and Jung^{24b} have demonstrated that iodotrimethylsilane under mild reaction conditions affords high yields of iodide from the corresponding alcohol. Under normal reaction conditions, iodotrimethylsilane generates HI in situ. This procedure would, therefore, preclude the use of acid labile functions. However, conversion of the alcohol to the trimethylsilyl derivative followed by reaction with iodotrimethylsilane provides an alternative route from alcohol to iodide without in situ generation of HI (Scheme III). Prior TMS derivatization is not

Scheme III



contingent for the conversion of primary, secondary, and tertiary alcohols to their corresponding iodides in good yields; rather, the conversion is dependent only on the alcohol itself. The fact that the conversion proceeds predominately with inversion of configuration is in accord with Jung's mechanism (Scheme IV).

Scheme IV

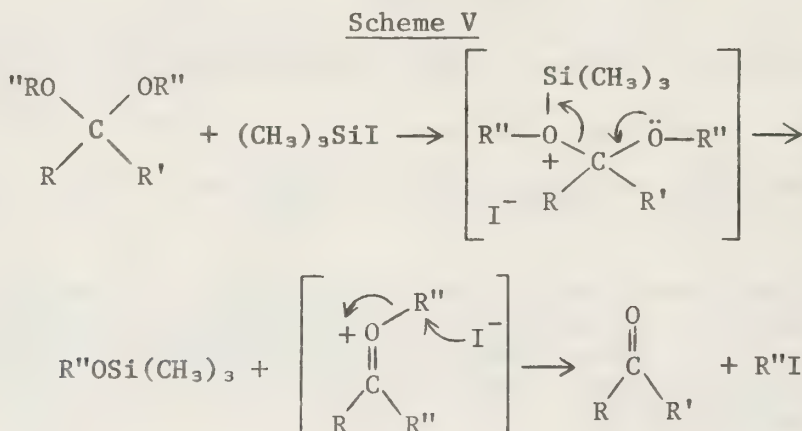


While many methods already exist for the deoxygenation of sulfoxides,²⁵ most rely on strong reductive conditions. A few use mild reaction conditions but yields are comparatively low. While investigating the synthetic potential of iodotrimethylsilane, Olah²⁶ found that iodotrimethylsilane could effectively deoxygenate sulfoxides under mild conditions with good yields. Both bromotrimethylsilane and iodotrimethylsilane react with sulfoxides, but the iodide is much more reactive. The mild conditions with the iodide have the distinct advantage of compatibility with other functional groups.

Conversion of ketals and acetals to their corresponding carbonyl derivatives is a necessary organic transformation. The standard method is mild acid-catalyzed aqueous hydrolysis. However, few methods are known for non-aqueous conversion to the carbonyl systems.^{8,27} Jung²⁸ has found that ketals and acetals, in the presence of iodotrimethylsilane,

readily undergo the transformation to ketones and aldehydes in good yields and under mild non-aqueous conditions. A special precaution is exercised in these conversions. Propene is added to the reaction mixture to eliminate the possibility of acid-catalyzed aldol condensations. Iodotrimethylsilane readily attacks dimethyl and diethyl ketals. Reactions with ethylene ketals and thioketals, on the other hand, result in complex mixtures or in no reaction. Ortho esters react cleanly with iodotrimethylsilane to yield carboxylic esters.

Certain functional groups are acid labile, such as trimethylsilyl enol esters, enol acetates, and alkyl enol ethers, but are stable to iodotrimethylsilane under the reaction conditions. This distinction, therefore, provides a means by which selective ketone formation can be achieved in the presence of appropriately protected ketones. Once again, due to the mild conditions, many different functional groups are compatible, such as ethers, esters, amines, amides, ketones, olefins, acetylenes, and halides. Very reactive functionality like alcohols, trityl, *t*-butyl, and benzyl ethers and esters, and epoxides would not be stable under these conditions. A possible mechanism has been proposed by Jung (Scheme V).



Physical data on the $(\text{CH}_3)_3\text{SiX}$ systems have been collected,²⁹ and theoretical arguments concerning the anomalous properties in the $(\text{CH}_3)_3\text{SiX}$ ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$) series are eloquently discussed by Van Der Kelen.³⁰ Van Der Kelen shows that the increasing dependence of ^{29}Si chemical shifts on the electronegativity of the halogen, when compared with the ^{13}C chemical shifts in alkyl halides, exhibits significant $p_x \rightarrow d_{\text{Si}}$ back donation which increases with increasing electronegativity of the halogen.

Several explanations for the ^{29}Si chemical shifts are offered. First, the σ^{E} and σ^{Anis} contributions might be important. Second, the intermolecular Van der Waals' forces between bulkier halogens and the methyl protons could strongly affect the C-H hybridization. Finally, hyperconjugative effects might be invoked.

The ^1H chemical shifts and both $^2\text{J}_{29\text{Si-H}}$ and $^1\text{J}_{13\text{C-H}}$ coupling constants (Table II) are inversely related to the electronegativity of the halogens. Schmidtbaur's explanation³¹ is that as the electronegativity increases, the $(p \rightarrow d)\pi$ back-bonding becomes the dominant effect. The immediate result of increased $(p \rightarrow d)\pi$ back-bonding ($\text{I} \rightarrow \text{F}$) is the equalization of the differences in electronegativity between halogens. This phenomenon is seen in ESCA studies.³² The experimentally determined binding energies between atoms shows only a slight increase ($\text{F} \rightarrow \text{I}$) for silicon. However, the binding energy for

Table II. Spectral Data on the Halogeno (methyl)-Silane Series

Compound	δ			J	
	^1H	^{13}C	^{29}Si	$^2J_{29}\text{Si-H}$	$^1J_{13}\text{C-H}$
<u>$(\text{CH}_3)_3\text{SiX}$</u>					
F	-	-0.32*	+32.01*	6.8*	118.5*
Cl	+0.23	+3.40*	+30.21	6.9	120.9
Br	+0.26	+4.55*	+26.41	7.0	121.4
I	+0.53	+6.50*	+ 8.72	7.1	121.8
<u>$(\text{CH}_3)_2\text{SiX}_2$</u>					
Cl	+0.43		+32.17	7.6	123.5
Br	+0.72		+19.86	7.6	124.2
I	+1.09		-33.68	7.4	124.7
<u>$(\text{CH}_3)_2\text{SiX}_3$</u>					
Cl	+0.57		+12.47	9.0	126.2
Br	+1.02		-18.18	8.6	126.9
I	+0.91		-17.96	8.5	126.4

*ref. 33

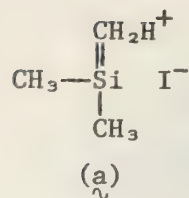
carbon is the same within experimental error. Therefore, the conclusion is that different halogens exhibit similar effects on the binding energies although their Pauling electronegativities vary considerably. The theory of total dependence on $(p \rightarrow d)\pi$ back-bonding does not explain the ^{29}Si and ^{13}C chemical shifts which correlate linearly with the halogen electronegativity values.

Another theory is that, if the $^2J_{29}\text{Si-H}$ coupling constants are proportional to the percent s character of the silicon atom in the Si-C orbital, variations should increase in going from chloride to iodide. This means a greater percentage of s character in the Si-X bond ($\text{Cl} \rightarrow \text{I}$). In opposition to this theory, an EESOP study by Drake^{32,33} shows qualitatively that the determined percent s character for $(\text{CH}_3)_3\text{SiX}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) is 5, 11, and 15% respectively. This hypothesis is invalid for it violates Bent's rules.³⁴

A further explanation of the anomalous physical properties of the $(\text{CH}_3)_3\text{SiX}$ compounds is that the molecule has undergone rehybridization in the Si-C orbitals by structural changes. The structural changes would be either opening of the C-Si-C angle or reduction of the C-Si-X angle in going from chloride to iodide. Unfortunately, insufficient accurate structural data are available. A reasonable comparison is possible between the $(\text{CH}_3)_3\text{SiX}$ series and the CH_3X series. The two systems exhibit similar trends in the $^{13}\text{C-H}$ coupling constants; however, more structural information is available for the CH_3X series.

When the trends in the $^{13}\text{C-H}$ coupling constants and the $^{29}\text{Si-C-H}$ coupling constants of the di- and tri-halides are examined, the variations suggest that C-H rehybridization is not induced in a similar fashion to Si-C rehybridization. An alternative explanation is that the change in the C-Si-X angle is caused by the contribution of a resonance structure (a) induced by either the hyperconjugative effects of the halogen or, more likely, from Van der Waals' repulsion effects between bulkier X atoms and methyl protons. The effect of the hyperconjugated structure is to cause

an increase in the ^{29}Si -C-H coupling constant with decreasing electronegativity. Structure (a) would result also in a reduction of the C-Si-X bond angle. This model successfully explains the ^1H chemical shifts in terms of the ^{29}Si -H and ^{13}C -H coupling constants. Therefore, it is not necessary to invoke a diamagnetic anisotropy effect of the Si-X bond. The possibility that such a contribution does not occur cannot, however, be completely discounted.



Finally, the proposed structure (a) can be used to explain qualitatively other unusual physical data. The hyperconjugative structure can explain the trends in both $(\text{CH}_3)_3\text{SiX}$ dipole moments³⁵ and force constants.³⁶ As the s character increases in the Si-C orbital ($\text{Cl} \rightarrow \text{I}$), which is induced by the increasing C-Si-C angle, there is a corresponding decrease in the magnitude of the C-Si moment which is opposite to the Si-X moment.

Iodotrimethylsilane continues to show promise as a highly useful synthetic reagent. The selectivity coupled with mild conditions and ease of work-up make iodotrimethylsilane a reagent of choice for many conversions. Further work is now being carried out to determine the full scope of reactions with iodotrimethylsilane.

BIBLIOGRAPHY

1. (a) R. L. Burwell, Jr., *Chem. Rev.*, **54**, 615 (1954); (b) C. A. Smith and J. B. Grutzner, *J. Org. Chem.*, **41**, 367 (1976).
2. (a) T. K. Brotherton and J. F. Bunnett, *Chem. Ind.*, **80** (1957); (b) S. Goodwin and E. C. Horning, *J. Am. Chem. Soc.*, **81**, 1908 (1959); (c) J. H. Chesterfield, J. F. W. McOmie, and M. S. Tute, *J. Chem. Soc.*, 4590 (1960); (d) B. Koutek and K. Setínek, *Collect. Czech. Chem. Commun.*, **33**, 866 (1968); (e) J. Gierer and B. Koutek, *Acta Chem. Scand.*, **23**, 1343 (1969); (f) I. T. Harrison, *Chem. Commun.*, 616 (1969); (g) J. W. Wildes, N. H. Martin, C. G. Pitt, and M. E. Wall, *J. Org. Chem.*, **36**, 721 (1971); (h) G. I. Feutrill and R. N. Mirrington, *Aust. J. Chem.*, **25**, 1719 (1972); (i) M. S. Newman, V. Sankaran, and D. R. Olsen, *J. Am. Chem. Soc.*, **98**, 3237 (1976).
3. (a) A. L. Wildes and W. B. McCormack, *J. Am. Chem. Soc.*, **70**, 4127 (1948); (b) W. S. Johnson, E. R. Rogier, and J. Ackerman, *J. Am. Chem. Soc.*, **78**, 6322 (1956); (c) D. J. Goldsmith, E. Kennedy, and R. G. Campbell, *J. Org. Chem.*, **40**, 3571 (1975).
4. F. G. Mann and M. J. Pragnell, *J. Chem. Soc.*, 4120 (1965).
5. (a) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 4153 (1966); (b) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968); (c) A. Brossi, M. F. Rahman, K. C. Rice, M. Gerecke, R. Borer, J. P. O'Brien, and S. Teitel, *Heterocycles*, **7**, 277 (1977).
6. H. Stone and H. Shechter, *Org. Syn. Col.*, Vol. IV, 321 (1963).
7. (a) A. J. Birch, *J. Chem. Soc.*, 102 (1947); (b) J. J. Eisch, *J. Org. Chem.*, **28**, 707 (1963); (c) K. H. Markiewicz and C. R. Dawson, *J. Org. Chem.*, **30**, 1610 (1965).
8. E. Winterfeldt, *Synthesis*, 617 (1975).

9. (a) L. I. Zakharkin, V. I. Stanko, and V. A. Brattesev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2079 (1961); (b) M. G. Voronkov, V. E. Puzanova, S. F. Parlov, and E. I. Dubinskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 377 (1975); (c) M. G. Voronkov, E. I. Dubinskaya, V. G. Komarov, and S. F. Parlov, *Zh. Obshch. Khim.*, 46, 1908 (1976); (d) M. G. Voronkov, E. I. Dubinskaya, S. F. Parlov, and V. G. Gorokhova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2198 (1976); (e) M. G. Voronkov, S. F. Parlov, E. I. Dubinskaya, *Dokl. Akad. Nauk SSSR*, 227, 218 (1976); (f) T. L. Ho and G. A. Olah, *Angew. Chem.*, 88, 847 (1976); (g) T. L. Ho and G. A. Olah, *Synthesis*, 417 (1977); (h) M. E. Jung and M. A. Lyster, *J. Org. Chem.*, 42, 3761 (1977); (i) B. I. Rosen and W. P. Weber, *J. Org. Chem.*, 42, 3463 (1977).
10. (a) J. C. Sheeland and G. D. Daves, Jr., *J. Org. Chem.*, 29, 2006 (1964); (b) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970); (c) J. E. McMurry and G. B. Wong, *Syn. Commun.*, 2, 389 (1972); (d) P. Müller and B. Siegfried, *Tetrahedron Lett.*, 3562 (1973); (e) T. L. Ho and C. M. Wong, *Syn. Commun.*, 4, 307 (1974); (f) T. L. Ho and C. M. Wong, *ibid.*, 5, 305 (1975).
11. E. W. Thomas and T. I. Crowell, *J. Org. Chem.*, 37, 744 (1972).
12. P. S. Manchand, *Chem. Commun.*, 667 (1971).
13. T. L. Ho and G. A. Olah, *Synthesis*, 418 (1977).
14. A. E. Greene, A. Cruz, and P. Crabbé, *Tetrahedron Lett.*, 2707 (1976).
15. Ch. Rav-Acha, M. Chevion, J. Katzhendler, and S. Sarel, *J. Org. Chem.*, 43, 591 (1978).
16. (a) T. L. Ho, *Synthesis*, 715 (1974); (b) T. L. Ho, *ibid.*, 510 (1975).
17. G. S. Burlachenko, Y. I. Barkov, T. G. Dzherayan, and I. F. Lutsenko, *Zh. Obshch. Khim.*, 45, 73 (1975).
18. (a) M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, 99, 968 (1977); (b) T. L. Ho and G. A. Olah, *Proc. Nat. Acad. Sci.*, 75, 4 (1978).
19. (a) W. W. Hartman, J. R. Byers, and J. B. Dickey, *Org. Syn. Col.*, Vol. II, 322 (1943); (b) H. S. King, *ibid.*, 399 (1943).
20. (a) H. Stone and H. Shechter, *J. Org. Chem.*, 15, 491 (1950); (b) H. Stone and H. Shechter, *Org. Syn. Col.*, Vol. IV, 323 (1963).
21. (a) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953); (b) D. G. Coe, S. R. Landauer, and H. N. Rydon, *ibid.*, 2281 (1954); (c) J. P. H. Vereyden and J. G. Moffatt, *J. Am. Chem. Soc.*, 86, 2093 (1964); (d) E. J. Corey and J. E. Anderson, *J. Org. Chem.*, 32, 4160 (1967); (e) J. P. H. Verheyden and J. G. Moffatt, *ibid.*, 35, 2319 (1970); (f) J. P. H. Verheyden and J. G. Moffatt, *ibid.*, 35, 2868 (1970); (g) H. N. Rydon, *Org. Syn.*, 51, 44 (1971).
22. (a) G. F. Freeguard and L. H. Long, *Chem. Ind. (London)*, 1582 (1964); (b) G. F. Freeguard and L. H. Long, *ibid.*, 223 (1965).
23. (a) D. N. Kevill and F. L. Wietl, *J. Org. Chem.*, 32, 2633 (1967); (b) T. W. Gibson and W. F. Erman, *J. Am. Chem. Soc.*, 91, 4771 (1969); (c) R. Scheffold and E. Saladin, *Angew. Chem.*, 84, 158 (1972).
24. (a) F. Piper and K. Rühlmann, *J. Organometal. Chem.*, 121, 149 (1976); (b) M. E. Jung and P. L. Ornstein, *Tetrahedron Lett.*, 2659 (1977).
25. (a) E. N. Karavlova and G. D. Gal'pern, *Zh. Obshch. Khim.*, 29, 3033 (1959); (b) D. Landini, F. Montanari, H. Hogereen, and G. Maccagnani, *Tetrahedron Lett.*, 2691 (1964); (c) K. Naumann, G. Zon, and K. Mislow, *J. Am. Chem. Soc.*, 91, 7012 (1969); (d) H. Alper and E. C. H. Keung, *Tetrahedron Lett.*, 53 (1970); (e) T. L. Ho and C. M. Wong, *Syn. Commun.*, 3, 37 (1973); (f) G. M. Gurria and G. H.

- Posner, J. Org. Chem., 38, 2419 (1973); (g) T. Aido, N. Furukawa, and S. Oae, Tetrahedron Lett., 3853 (1973); (h) T. L. Ho and C. M. Wong, Synthesis, 206 (1973); (i) H. D. Durst, J. W. Zubrick, and G. R. Kieczkowski, Tetrahedron Lett., 1777 (1974); (j) K. Ogura, M. Yamashita, and G. Tsuchihashi, Synthesis, 385 (1975); (k) G. A. Olah, G. K. S. Prakash, and T. L. Ho, *ibid.*, 810 (1976); (l) D. W. Chasar and T. M. Pratt, *ibid.*, 262 (1976); (m) J. Drabowicz and S. Oae, Synthesis, 404 (1977); (n) I. W. J. Still, S. K. Hasan, and K. Tutnbull, *ibid.*, 468 (1977).
26. G. A. Olah, B. G. B. Gupta, and S. C. Narang, *ibid.*, 583 (1977).
27. (a) A. Bowers, L. C. Ibáñez, and H. J. Ringold, Tetrahedron, 7, 138 (1959); (b) R. Furstoss, R. Tadayoni, G. Esposito, J. Lacrampe, A. Hermann, and B. Waegell, Can. J. Chem., 54, 3569 (1976); (c) G. B. Butler, K. H. Herring, P. L. Lewis, V. V. Sharpe III, and R. L. Venzey, J. Org. Chem., 42, 679 (1977).
28. M. E. Jung, W. A. Andrus, and P. L. Ornstein, Tetrahedron Lett., 4175 (1977).
29. (a) T. Shimanouchi, I. Tsuchiya, and Y. Mikawa, J. Chem. Phys., 18, 1306 (1950); (b) J. D. Gile, W. M. Garrison, and J. G. Hamilton, J. Chem. Phys., 19, 1217 (1951); (c) H. Kriegsmann, Z. Anorg. Allg. Chem., 294, 113 (1958); (d) K. Shimizu and H. Murata, J. Mol. Spectrosc., 4, 201 (1960); (e) M. Murray, G. Schirawski, and U. Wannagat, J. Chem. Soc., Dalton Trans., 911 (1972); (f) H. Schmidt baur and W. Vornberger, Chem. Ber., 105, 3173 (1972); (g) G. Englehardt, R. Radeaglia, H. Jancke, E. Lippmaa, and M. Maggi, Org. Mag. Res., 5, 561 (1973); (h) H. Schmidt baur and R. Seeber, Chem. Ber., 107, 1731 (1974).
30. E. V. Van Den Berghe and G. P. Van Der Kelen, J. Organometal. Chem., 59, 175 (1973).
31. H. Schmidt baur, J. Am. Chem. Soc., 85, 2336 (1963).
32. (a) J. E. Drake, C. Riddle, and L. Coatsworth, Can. J. Chem., 53, 3602 (1975); (b) J. E. Drake, C. Riddle, H. E. Henderson, and B. Glavincerski, *ibid.*, 54, 3876 (1976).
33. R. K. Harris and B. J. Kimber, J. Mag. Res., 17, 174 (1975).
34. (a) H. A. Bent, J. Chem. Educ., 37, 616 (1960); (b) H. A. Bent, J. Chem. Phys., 33, 1258 (1960); (c) H. A. Bent, Chem. Rev., 61, 276 (1961).
35. J. Goubeau and H. Sommer, Z. Anorg. Allg. Chem., 289, 1 (1957).
36. H. Bürger, Spectrochim. Acta, 24A, 2015 (1968).

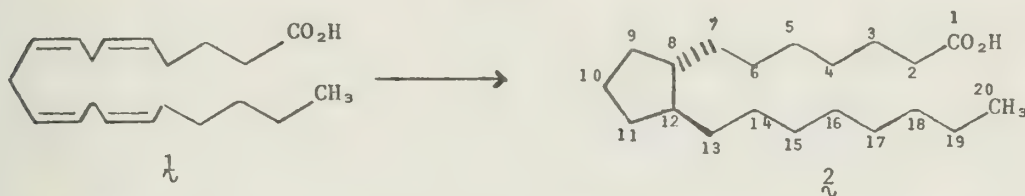
PROSTACYCLIN: CHEMISTRY, BIOSYNTHESIS, MOLECULAR PHYSIOLOGY

Reported by Stephen G. Senderoff

April 17, 1978

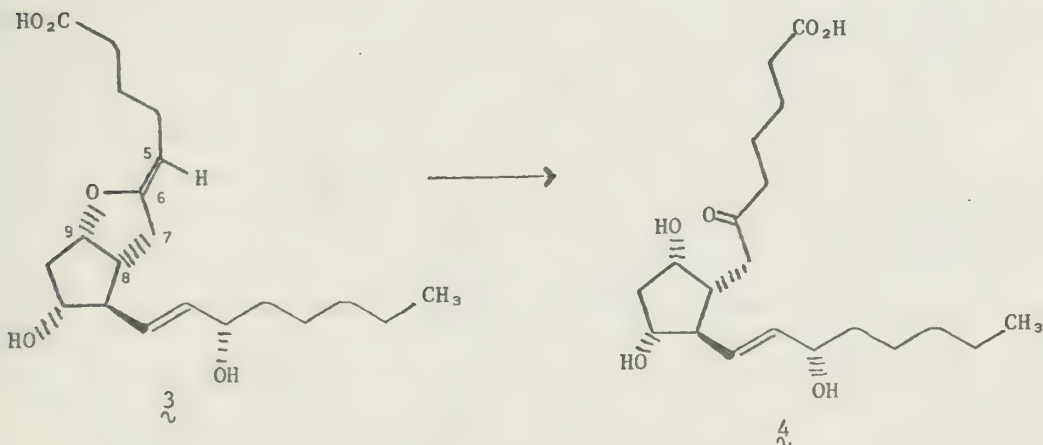
The prostaglandins are a group of acetate-derived natural products which possess the prostanoid acid carbon skeleton 2 as a common structural feature. The immediate biosynthetic precursors to these compounds are three unsaturated C-20 fatty acids, the most important being arachidonic acid 1. The prostaglandins are characterized by high activity and potency in numerous biological systems. Although prostaglandin-like bioactivity was noted in the early thirties, it was not until the late fifties that the compounds were isolated and their structures determined. Since this monumental work by Bergstrom and Samuelsson, the prostaglandins have been shown to be ubiquitous throughout all levels of the animal kingdom and involved in most of the biological processes of the organisms within this kingdom. The subsequent expansion of the field was unprecedented in both scope and breadth. Nevertheless, the biological function of the prostaglandins remains an enigma.¹

Figure 1



In the latter part of 1976, Vane and Needleman independently observed a hitherto unreported enzymatic transformation of arachidonic acid in vascular tissue, producing an unknown, extremely labile bioactive principle.² The unknown prostaglandin, then called PGX, had biological activity upon the circulatory system of mammals of a potency never before observed in prostanoid compounds. The characterization of this unknown prostaglandin allowed a unified mechanism to be proposed for the maintenance of circulatory homeostasis involving prostaglandins and prostaglandin biosynthetic intermediates. This seminar will review the research activity in the fields of synthetic organic chemistry, biosynthesis, and biology generated by the discovery of PGX, now called PGI₂ or prostacyclin.

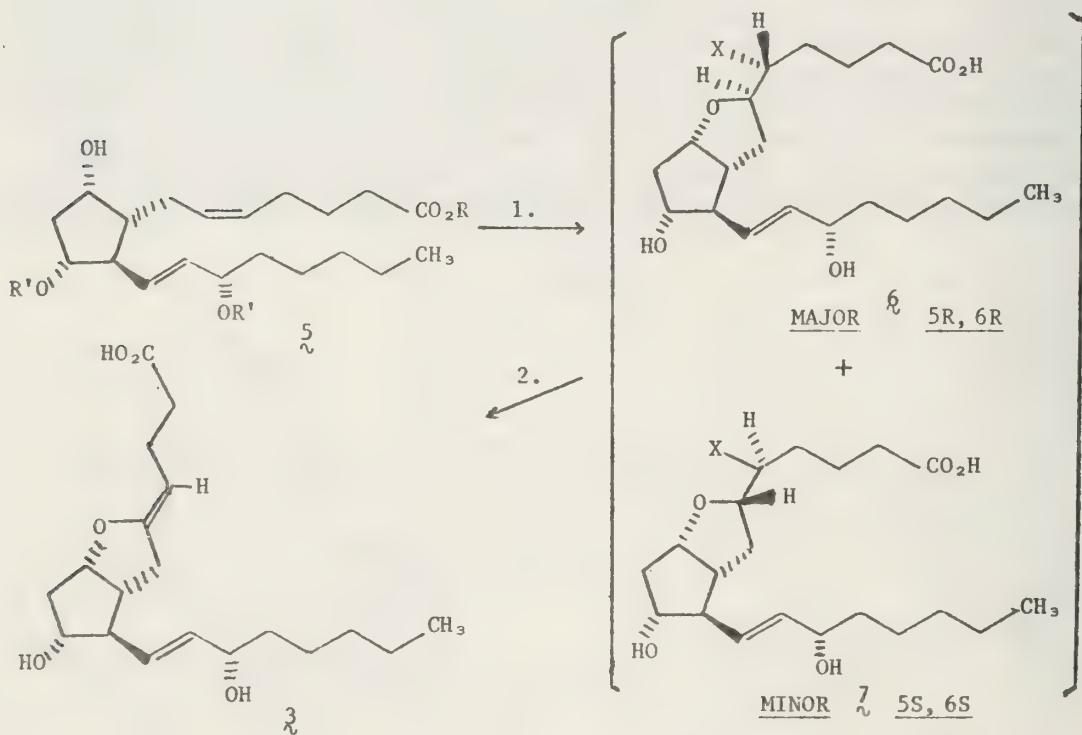
Figure 2



Prostacyclin is a bicyclic prostaglandin possessing a 6,9-epoxy bridge and a 5,6-double bond carrying the Z geometry as in **3**. This enolic ether is readily hydrolyzed in aqueous media to afford 6-keto PGF_{1α} (**4**). Although there have been reports of bicyclic prostaglandins³ and 6-keto PGF_{1α}⁴ since the early seventies, these compounds were considered to be uninteresting deviations from the normal pathways of arachidonic acid metabolism. The discovery that 6-keto PGF_{1α} was the major prostaglandin produced by various tissues and was the degradation product of a highly bioactive principle caused a burst of activity directed toward characterizing this "novel" metabolic pathway and its products. Biosynthetic considerations and gas chromatographic-mass spectrometric data afforded a nearly complete structure for prostacyclin, lacking only the identification of the 5,6-double bond geometry.⁵ The confirmation of the structure and the double bond geometry were provided by total synthesis.

Synthetic Chemistry. All of the total syntheses of prostacyclin take advantage of the facile cyclization resulting from intramolecular attack of the 9α-oxygen upon the 6-carbon of a 5,6-bridged halonium intermediate formed from halogenation of PGF_{2α} as shown in Scheme I. Intramolecular halohydrin reactions of this type are well documented.⁶ Subsequent dehydrohalogenation of the halo ether intermediate affords prostacyclin. The mechanism for the intramolecular halohydrin reaction dictates that the attack of the 9α-oxygen and addition of the halide must proceed in a trans manner, producing two stereoisomers about carbons 5 and 6 bearing the R,R and S,S configurations, respectively. Elimination of hydrogen halide from either of the two enantiomers should afford the proper Z geometry about the 5,6-double bond, for the elimination must proceed in a trans coplanar manner.

Scheme I



COREY: R = H, R' = THP, X = Br

JOHNSON: R = CH₃, R' = H, X = I

The apparent simplicity of this route to prostacyclin proved to be deceptive. The assignment of the correct stereochemistry to the two halo ether intermediates proved to be a formidable task. Careful studies of elimination reactions of both of the halo ether intermediates revealed interesting reactivity dependence upon stereochemistry at carbons 5 and 6, leading to prostacyclin or double-bond positional isomers of prostacyclin.

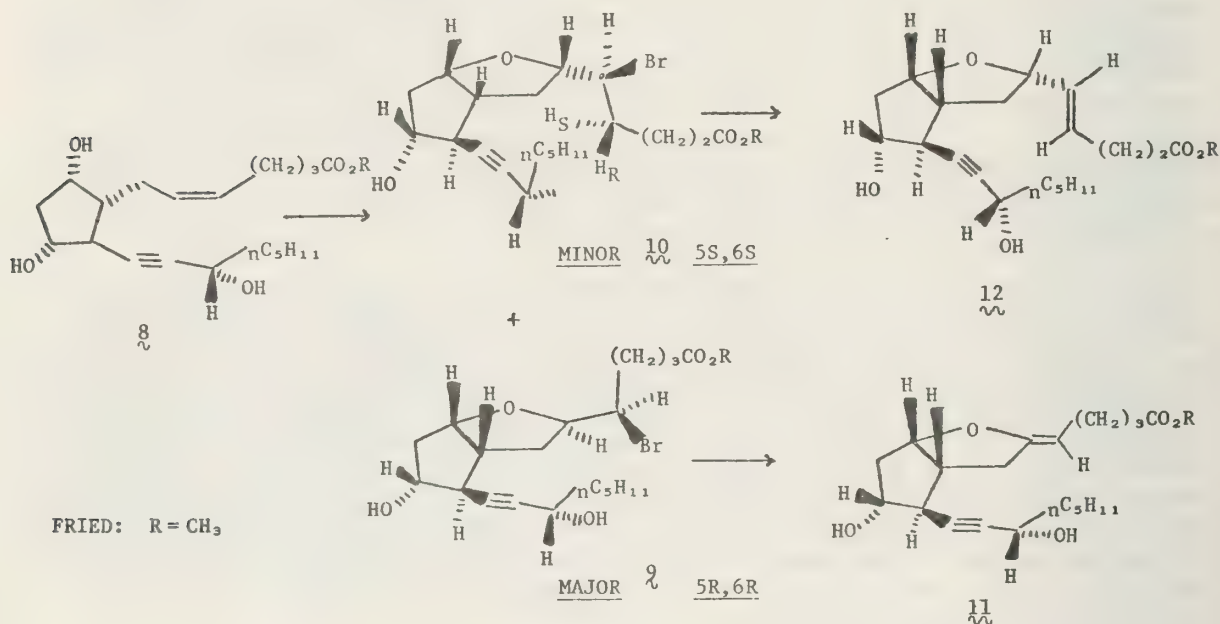
The first total synthesis of prostacyclin was accomplished by Corey. Treatment of the 11,15-bis THP ether of $\text{PGF}_{2\alpha}$ **5** with NBS followed by depyranylation afforded a mixture of stereoisomeric bromo ethers **6** and **7** separable by thin layer chromatography. The major bromo ether having the lower R_f value afforded prostacyclin **3** upon treatment with potassium *t*-butoxide in *t*-butanol. The minor bromo ether failed to react under these conditions. Corey assigned the 5*S*,6*S* and the 5*R*,6*R* configurations to the major and minor products, respectively, rationalizing that the *exo* 6-proton of the *S,S* stereoisomer was more accessible to base than the more hindered *endo* 6-proton of the *R,R* stereoisomer.⁸ Similar conclusions were drawn by Kovacs in a later total synthesis.⁹ However, data at variance with these assignments was forthcoming.

A total synthesis of prostacyclin by Johnson was accomplished by dehydrohalogenation of the major iodo ether intermediate produced from $\text{PGF}_{2\alpha}$ methyl ester by treatment with molecular iodine. The base effecting the elimination was DBN. Johnson assigned the 5*R*,6*R* stereochemistry to the major iodo ether **6** on the basis of expected transition state energies leading to the *R,R* or *S,S* products. Consideration of molecular models showed the transition state leading to the *R,R* stereoisomer to possess a less crowded molecular geometry than the transition state leading to the *S,S* stereoisomer. The lower energy of the transition state leading to the *R,R* product then dictates a preponderance of this compound in the reaction mixture at completion.¹⁰

Further support for Johnson's stereochemical assignments was obtained by the total synthesis of 13,14-dehydro prostacyclin methyl ester by Fried. Treatment of the 13,14-dehydro methyl ester of $\text{PGF}_{2\alpha}$ **8** with NBS in acetonitrile afforded stereoisomeric bromo ethers **9** and **10**, the lower and higher R_f components occurring in a 4:1 ratio, respectively. Fried assigned the 5*R*,6*R* configuration to the major bromo ether **9** using a transition state energy argument identical to that of Johnson. The two stereoisomers also had strikingly different reactivities upon treatment with DBU in toluene. Elimination of hydrogen halide from **9** afforded 13,14-dehydro prostacyclin methyl ester **11**, while identical treatment of the *S,S* halo ether **10** afforded a double bond positional isomer **12**. One would expect these patterns of reactivity to be reversed on the basis of the relative accessibility of the 6-proton in each stereoisomer to external base. The 5*S*,6*S* isomer carries the 6-proton in the relatively unhindered *exo* orientation to the oxabicyclo[3.3.0]octane ring, while the 5*R*,6*R* compound carries this proton in the relatively hindered *endo* orientation. External base would be expected to encounter steric interference upon attacking the 6-proton of the 5*R*,6*R* stereoisomer. Attack upon a 4-proton and subsequent halide expulsion would appear to be favored, affording **12**. By the same logic, the *S,S* isomer should afford **11** on the basis of its accessible 6-proton. The observed reactivity may be explained by invoking attack of the deprotonated 11 α -hydroxyl upon the C-4 *pro-S* hydrogen of **10** in an intramolecular fashion. Subsequent halide expulsion affords **12**. The 5*R*,6*R* compound **9** would not react in this manner, for the

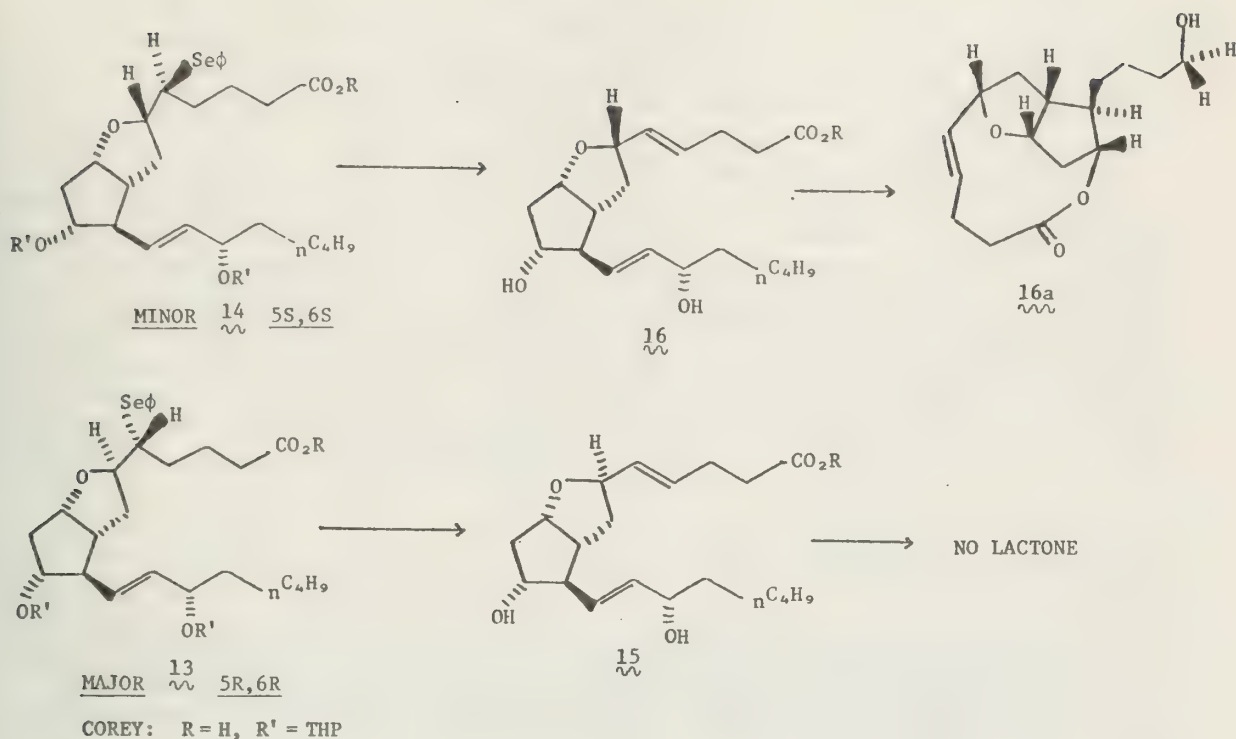
C-6 side chain is carried in the exo orientation. This notion was supported by treatment of the 11,15-bis-methoxymethyl ethers of 9 and 10 with DBU and isolation of 13,14-dehydro prostacyclin methyl ester from both reactions after deetherification. This finding implicates the intramolecular participation of the 11 α -hydroxyl group in the formation of 12 from 10, and demonstrates that the accessibility of the 6-proton in either stereoisomer is not a factor in determining the direction of elimination. Scheme II summarizes Fried's work.¹¹

Scheme II



Although the stereochemistry and structure of natural prostacyclin had been confirmed, it was apparent that the stereochemical identity of the halo ether intermediates 6 and 7 was uncertain. Later experiments by Corey offered definitive answers to this question. The minor phenyl seleno ether 14 formed from the 11,15-bis-THP ether of PGF₂ α was lactonized to 16a as shown in Scheme III. The major phenyl seleno ether 13 afforded no lactone under identical conditions. Consideration of the orientation of the C-6 side chain in each phenyl seleno ether precludes lactone formation from 13 and identifies 14 as possessing the 5S,6S configuration.¹² Further support for these assignments was provided by the work of Tomoskoszi¹³ and Nelson.¹⁴ Two other total syntheses of prostacyclin have been reported by Whittaker¹⁵ and Nicolaou.¹⁶ Both syntheses employ the route outlined in Scheme I.

Scheme III

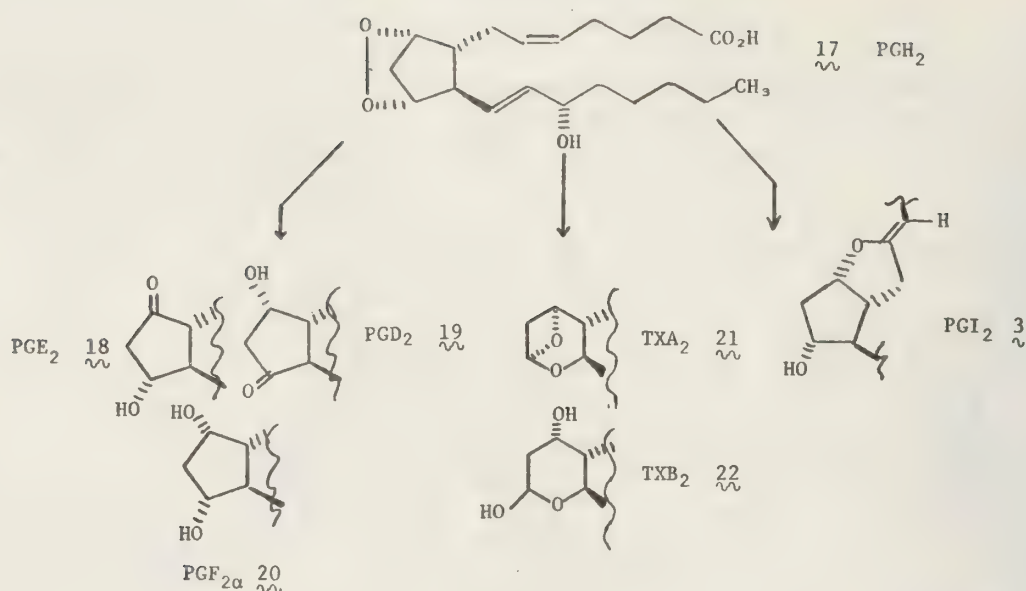


The total synthesis of prostacyclin was undertaken to determine its structure unambiguously and to provide material urgently needed for biological testing. A deeper appreciation of the biological importance of prostacyclin may be obtained by the consideration of the biosynthesis of the '2' series of prostaglandins from arachidonic acid.¹⁷ Since nearly all of the biosynthetic intermediates in the production of these prostaglandins possess marked bioactivity,¹⁸ interactions between end products and intermediates become of great importance when considering the physiological role of a prostaglandin.

Biosynthesis. Scheme IV outlines the well known biosynthesis of prostaglandins from arachidonic acid. The key intermediates are the prostaglandin endoperoxides, PGG₂ and PGH₂.¹⁹ Both endoperoxides are potent agents causing platelet aggregation and vasoconstriction. They are formed from arachidonic acid by the enzyme fatty acid cyclo-oxygenase, an enzyme that has been the object of intense study in recent years.²⁰

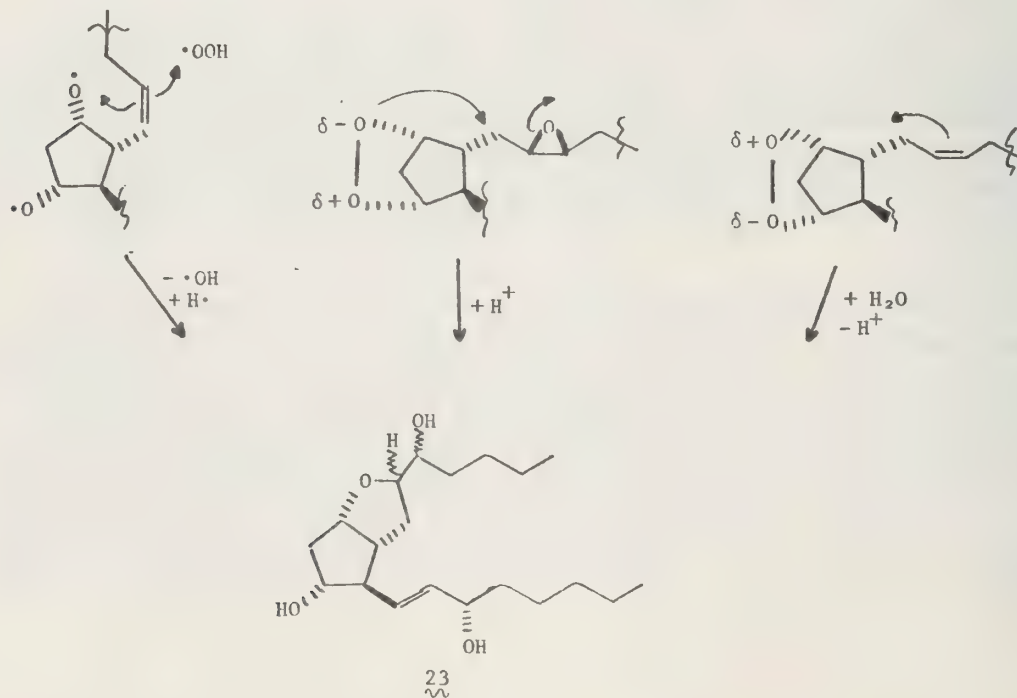
The prostaglandin endoperoxides serve as substrates to three enzymatic pathways. Isomerization or reduction of the endoperoxide PGH affords the primary prostaglandins PGD₂, PGE₂, and PGF_{2α}. The primary biological effects of these compounds are not upon the circulatory system. A second pathway from PGH₂ affords the very labile thromboxane (TX) A₂, which is quickly hydrolyzed to TXB₂. Thromboxane A₂ has bioactivity similar to the prostaglandin endoperoxides, but is much more potent. The details of the biosynthesis of the thromboxanes have been discussed elsewhere,^{18,21} The third pathway from PGH₂ leads to prostacyclin.

Scheme IV



Prostacyclin may be envisioned to arise from free radical attack of the 9 α oxygen upon the 5,6-double bond of PGH₂ in an intramolecular fashion after homolytic fragmentation of the endoperoxide oxygen-oxygen bond. Carbon-oxygen bond formation at C-6 followed by loss of a hydrogen radical at C-5 affords prostacyclin.²² Alternatively, an intermediate 6,9 α -epoxy-5-hydroxy compound 23 may be enzymatically dehydrated to afford prostacyclin. Scheme V illustrates how this intermediate may be formed by both free radical and dipolar mechanisms. However, careful experiments by Sih demonstrated that 23 was not a free intermediate in prostacyclin biosynthesis.²³ Pace-Asciak has proposed an enzyme-bound intermediate similar to 23.²⁴

Scheme V



Molecular Physiology. Prostacyclin synthetase generates prostacyclin in a variety of mammalian tissues, notably the rabbit uterus, bovine corpus luteum, porcine and ovine aorta,¹⁸ rabbit and rat heart,²⁵ bovine iris-ciliary body,²⁶ rat stomach,²⁴ and human renal cortical microsomes.^{27,29} Although the role of prostacyclin in most of these tissues is unknown, intense research has afforded a correlation between the observed biological effects of prostacyclin and a possible physiological role in the circulatory system. Prostacyclin inhibits blood platelet aggregation,²⁸ reverses the aggregation of previously aggregated platelets,³³ relaxes the coronary artery, and lowers blood pressure in mammals.²⁸ This activity is directly antagonistic to that of the thromboxanes. Since both of these compounds are derived from a common intermediate, they may comprise a powerful circulatory homeostatic mechanism responsible for the maintenance of normal blood flow, normal blood pressure, and providing protection against vascular injury. A deeper understanding of this mechanism is afforded by a brief review of blood platelet function and its relation to the most common circulatory disorder, atherosclerosis.^{30,31}

The main function of the blood platelets is the control of blood loss. The platelets aggregate at the site of vascular injury, preventing blood loss and maintaining blood pressure. Platelets will not adhere to vessel walls or each other in the absence of injury. Platelet aggregation occurs in two phases. Small amounts of vascular collagen exposed as a result of damage to the blood vessel cause the platelets to aggregate in a mild, reversible manner. This aggregation causes the release of compounds (notably prostaglandin endoperoxides^{30,32}) from the interior of the platelets. This release causes a wide-spread, intense, irreversible wave of aggregation, completing the platelet response to injury.

The platelet response mechanism is central to the understanding of the pathogenesis of atherosclerosis a disease characterized by the blocking of arteries with dense plugs of fat and connective tissue. Injury to the innermost layer of the artery exposes vascular collagen, causing platelet aggregation at the site of injury. The release of compounds from the platelets causes vascular smooth muscle to grow into the area of injury. Subsequent deposition of fat and collagen eventually blocks the artery.

The control of these processes by the prostacyclin-thromboxane homeostatic mechanism is envisioned as follows: the prostaglandin endoperoxides released by the platelets are converted to TXA₂ by platelet thromboxane synthetase. The thromboxane alone, or in concert with the endoperoxide, may initiate irreversible platelet aggregation, but the generation of prostacyclin from the endoperoxide by blood vessel prostacyclin synthetase³⁴ prevents aggregation. The delicate balance between the activities of these compounds maintains circulatory homeostasis, or status quo.²⁸

Atherosclerosis may be seen to arise as a result of decreased prostacyclin production by the vascular walls. This idea is supported by the observation of decreased prostacyclin levels associated with atherosclerosis generated experimentally in rats.³⁵ Another process leading to the inactivation of prostacyclin synthetase is lipid peroxidation. It has been demonstrated that 15-hydroperoxy arachidonic acid is a potent inhibitor of prostacyclin synthetase.³⁶ This lipid hydroperoxide is produced non-enzymatically in blood plasma as part of the aging process. This finding lends credibility to the hypothesis that anti-oxidants such as Vitamin E prevent the occurrence of circulatory disorders.

Although the exact mechanism by which prostacyclin acts upon blood platelets is unknown, the compound has been observed to cause marked elevation of intracellular cAMP levels. Future research will provide a unified mechanism for circulatory homeostasis involving prostaglandins and cyclic nucleotides.^{37,38} It is also possible that prostaglandin-cyclic nucleotide systems will be involved in the maintenance of the integrity of other tissues in which prostacyclin and thromboxane generating systems are found.

It is apparent that prostacyclin-like pharmacological activity may be employed in the treatment of thrombo-embolic disorders of the circulatory system in man, but prostacyclin itself is unsuitable for this role because of its great lability. Organic chemists have been concerned with the synthesis of prostacyclin analogues possessing platelet anti-aggregatory and vasodilatory activity along with greater stability under physiological conditions. Active workers in this area include Corey,³⁹ Fried,⁴⁰ Nicolaou,⁴¹ and Ikegami.⁴² The most promising compound so far is 6,9-thiaprostacyclin, showing the expected resistance to hydrolysis and platelet aggregation inhibitory activity. Interestingly, 6,9-thiaprostacyclin is a vasoconstrictor.⁴¹

BIBLIOGRAPHY

1. For general reviews of prostaglandin research, see (a) P. Ramwell, ed., "The Prostaglandins", Vol. 1- , Plenum Press, New York, 1972- ; (b) P. Crabbe, ed., "Prostaglandin Research", Academic Press, New York, 1977; (c) J. Lee, Ed., "Perspectives on the Prostaglandins", Medcom, Inc., New York, 1973.
2. (a) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 263, 663 (1976); (b) A. Raz, P. Isakson, M. Minkes, and P. Needleman, *J. Biol. Chem.*, 252, 1123 (1977); (c) P. C. Isakson, A. Raz, S. Denney, E. Pure, and P. Needleman, *Proc. Nat. Acad. Sci. U.S.*, 74, 101 (1977).
3. C. Pace-Asciak and L. Wolfe, *Biochemistry*, 10, 3657 (1971).
4. (a) C. Pace-Asciak, *Experientia*, 32, 291 (1976); (b) C. Pace-Asciak, *J. Am. Chem. Soc.*, 98, 2348 (1976).
5. R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, and J. Salom, *Prostaglandins*, 12, 915 (1976).
6. H. Wong, J. Chapuis, and I. Monkovic, *J. Org. Chem.*, 39, 1024 (1974).
7. E. J. Corey, N. Weinshenker, T. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, 91, 5675 (1969).
8. E. J. Corey, G. Keck, and I. Szekely, *J. Am. Chem. Soc.*, 98, 2006 (1976).
9. I. Tomoskozi, G. Galambos, V. Simonidesz, and G. Kovacs, *Tetrahedron Lett.*, 2627 (1977).
10. R. Johnson, F. Lincoln, J. Thompson, E. Nidy, S. Miszak, and U. Axen, *J. Am. Chem. Soc.*, 99, 4184 (1977).
11. J. Fried and J. Barton, *Proc. Nat. Acad. Sci. U.S.*, 74, 2199 (1977).
12. E. J. Corey, personal communication.
13. I. Tomoskozi, G. Galambos, G. Kovacs, and L. Radics, *Tetrahedron Lett.*, 581 (1978).
14. N. A. Nelson, *J. Am. Chem. Soc.*, 99, 7362 (1977).
15. N. Whittaker, *Tetrahedron Lett.*, 2805 (1977).
16. K. C. Nicolaou, W. E. Barnette, G. P. Gasic, R. A. Magolda, and W. J. Sipio, *J. C. S. Chem. Commun.*, 630 (1977).
17. For a recent review of prostaglandin biosynthesis, see M. Hamberg and B. Samuelsson in "Molecular Mechanisms of Oxygen Activation", O. Hayaishi, ed., Academic Press, New York, 1974.

18. F. F. Sun, J. P. Chapman, and J. C. McGuire, *Prostaglandins*, 14, 1055 (1977).
19. A. M. Hamberg and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.*, 70, 899 (1973), 71, 345,3400 (1974); (b) D. Nugteren and E. Hazelhoff, *Biochim. Biophys. Acta*, 448 (1973).
20. (a) M. Hemler, W. E. M. Lands, and W. L. Smith, *J. Biol. Chem.*, 251, 5575 (1976); (b) M. Hemler and W. Lands, *Lipids*, 12, 591 (1977); (c) P. Gund and T. Y. Shen, *J. Med. Chem.*, 20, 1146 (1977).
21. M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.*, 72, 2994 (1975).
22. J. A. Turner and W. Herz, *Experientia*, 33, 1133 (1977).
23. F. C. Huang, M. Zmijewski, G. Girdaukas, and C. H. Sih, *Bioorganic Chem.*, 6, 311 (1977).
24. C. Pace-Asciak, and M. Nashat, *Biochim. Biophys. Acta*, 487, 495 (1977).
25. E. DeDeckere, D. Nugteren, and F. TenHoor, *Nature*, 268, 160 (1977).
26. P. Kulkarni, H. Eakins, W. Saber, and K. Eakins, *Prostaglandins*, 14, 689 (1977).
27. A. Whorton, M. Smigel, J. Oates, and J. Frolich, *Prostaglandins*, 13, 1021 (1977).
28. (a) R. Gryglewski, S. Bunting, S. Moncada, R. Flower, and J. R. Vane, *Prostaglandins*, 12, 685 (1976); (b) S. Bunting, R. Gryglewski, S. Moncada, and J. R. Vane, *ibid.*, 12, 897 (1976); (c) C. Omni, S. Moncada, and J. R. Vane, *ibid.*, 14, 625 (1977); (d) G. Dusting, S. Moncada, and J. R. Vane, *ibid.*, 13, 3 (1977); (e) S. Moncada, E. Higgs, and J. R. Vane, *The Lancet*, 18 (1977); (f) L. Myatt and M. Elder, *Nature*, 268, 159 (1977).
29. P. Bolger, G. Eisner, P. W. Ramwell, L. Slotkoff, and E. J. Corey, *Nature*, 271, 467 (1978).
30. For a review of platelet physiology, function and response to prostaglandins prior to the discovery of prostacyclin, see J. B. Smith and D. E. MacFarlane in "The Prostaglandins", Vol. II, P. Ramwell, ed., Plenum Press, New York, 1974, pp. 293-343.
31. For a review of the pathogenesis of atherosclerosis, see R. Ross and J. A. Glomset, *The New England Journal of Medicine*, 295, 369, 420 (1975).
32. G. Roth, N. Stanford, and P. J. Majerus, *Proc. Nat. Acad. Sci. U.S.*, 72, 3073 (1975).
33. P. P. K. Ho, R. G. Hermann, R. Towner, and C. Walters, *Biochim. Biophys. Acta*, 74, 514 (1977).
34. D. MacIntyre, J. Pearson, and J. L. Gordon, *Nature*, 271, 549 (1978).
35. A. Dembinska-Kiec, T. Gryglewska, A. Zmuda, and R. J. Gryglewski, *Prostaglandins*, 14, 1025, 1035 (1977).
36. S. Moncada, R. J. Gryglewski, and J. R. Vane, *Prostaglandins*, 12, 715 (1976).
37. (a) L. Best, T. Martin, R. Russel, and F. E. Preston, *Nature*, 267, 850 (1977); (b) E. Lapetina, C. Schmitges, K. Chandrabose, and P. Cuatrecasas, *Biochem. Biophys. Res. Comm.*, 76, 828 (1977); (c) R. Gorman, S. Bunting, and O. Miller, *Prostaglandins*, 13, 377 (1977); (d) J. E. Tateson, S. Moncada, and J. R. Vane, *ibid.*, 13, 389 (1977).
38. J. M. Gerrard, J. Peller, T. Krick, and J. G. White, *Prostaglandins*, 14, 39 (1977).
39. (a) E. J. Corey, I. Szekely, and C. Shiner, *Tetrahedron Lett.*, 3529 (1977); (b) E. J. Corey, personal communication.
40. P. Paustian, B. Chapnick, L. Fiegen, A. Hyman, P. Kadowitz, J. Fried, and J. Barton, *Prostaglandins*, 14, 1141 (1977).
41. (a) K. C. Nicolaou, W. E. Barnette, G. Gasic, and R. Magolda, *J. Am. Chem. Soc.*, 99, 7736 (1977); (b) K. C. Nicolaou, personal communication.
42. M. Shibasaki and S. Ikegami, *Tetrahedron Lett.*, 529 (1978).

OLEFINIC AND AROMATIC PALLADATIONS IN ORGANIC SYNTHESIS

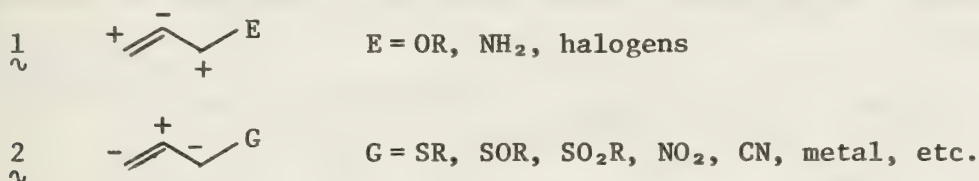
Reported by John S. Ng

April 20, 1978

Since the discovery of ferrocene in 1951, organic chemists have realized that many organotransition metal compounds are surprisingly air- and moisture-stable and can be used as important intermediates in organic synthesis. This seminar will deal with a group of reactions mediated by palladium, namely the palladations of olefinic and aromatic systems and their important applications in organic synthesis.

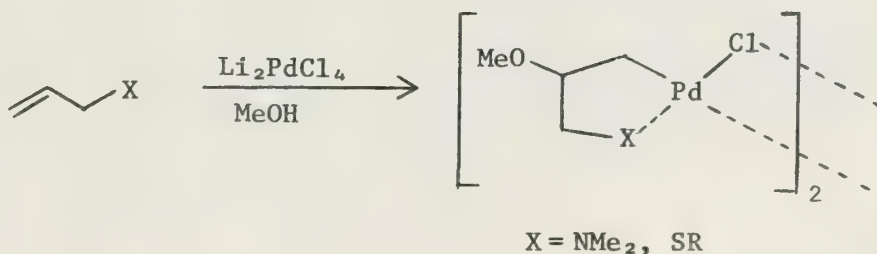
Carbopalladations and Depalladations of Allylic Amines and Sulfides.

The functions of allylic units in the construction of many organic molecules have been well demonstrated. The nucleophilic and electrophilic site reactivity of an allylic moiety may be governed by a terminally attached activating functionality. Using the Evan's convention,¹ we can have two main types of allylic systems, with the following anticipated polarities at each site:

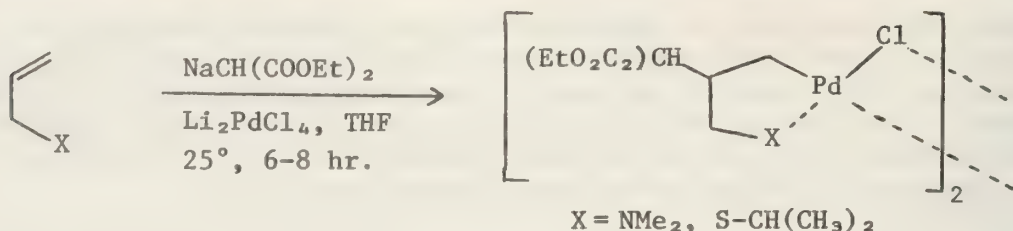


Nucleophilic substitution of substrates such as $\underset{\sim}{1}$ at either α or γ position is common; reaction of $\underset{\sim}{1}$ with electrophiles at the β carbon has been achieved via metallation;² α and γ alkylations of $\underset{\sim}{2}$ have recently been accomplished through metallated allylic sulfoxides,^{1,3a} sulfides,^{3b-1} and boranes.^{3m} Similar α and γ alkylations of $\underset{\sim}{1}$ have been achieved by a polarity inversion involving lithiation of allylic ethers^{4a-d} and amines.^{4e-g} However, carbon-carbon bond formation using the potentially electrophilic β carbon as in $\underset{\sim}{2}$ was not well known.

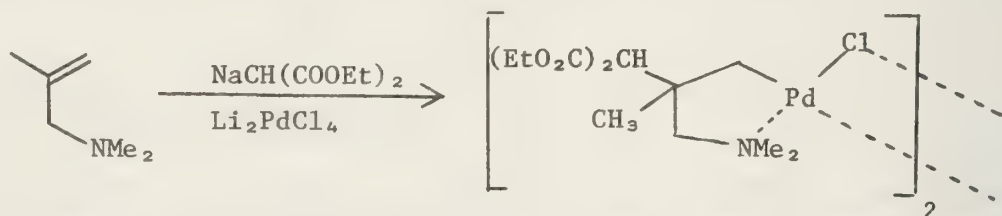
In 1977, Holton of Purdue University developed an efficient method for regiospecific attachment of carbon nucleophiles to the β carbon of allylic sulfides and amines,⁵ hence providing the experimental fulfillment of the anticipated reactivity of the β carbon in species like $\underset{\sim}{2}$ and providing in addition a synthetic method for polarity inversion at the β carbon in species like $\underset{\sim}{1}$. His approach involved an activation of the allylic units by complexing to palladium and the simultaneous attack of carbon nucleophiles at the β carbon. Earlier, Tsuji⁶ and others⁷ had observed the addition of sodiodiethylmalonate to 1,5-cyclooctadiene palladium chloride complex. Later,^{32,33} it was found that reaction of N,N-dimethylallylamine and allyl methyl sulfide with lithium tetrachloropalladate in methanol produced the following complexes:



Inspired by these results, Holton found that carbon nucleophiles can be added to allylic sulfides and amines in the presence of lithium tetrachloropalladate in high yields in a regiospecific manner; for example:

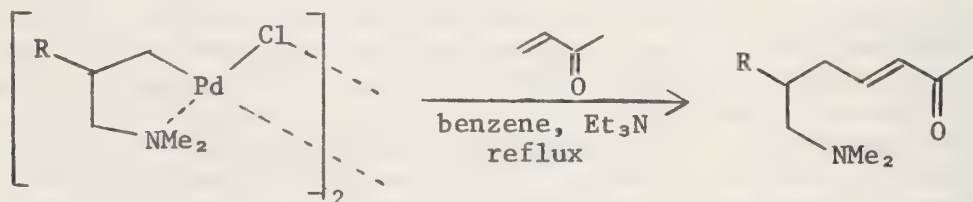


Other β -dicarbonyl enolates were also used to produce various complexes in yields of 80-95%. In addition to the high yields, these reactions also enjoy the advantage that the products are yellow crystals which are air- and moisture-stable and can be easily purified. Moreover, their formation seemed to be quite insensitive to steric crowding. For example, reaction of 3-dimethylamino-2-methylpropene with sodio-malonic ester and lithium tetrachloropalladate still gave rise to the following complex:

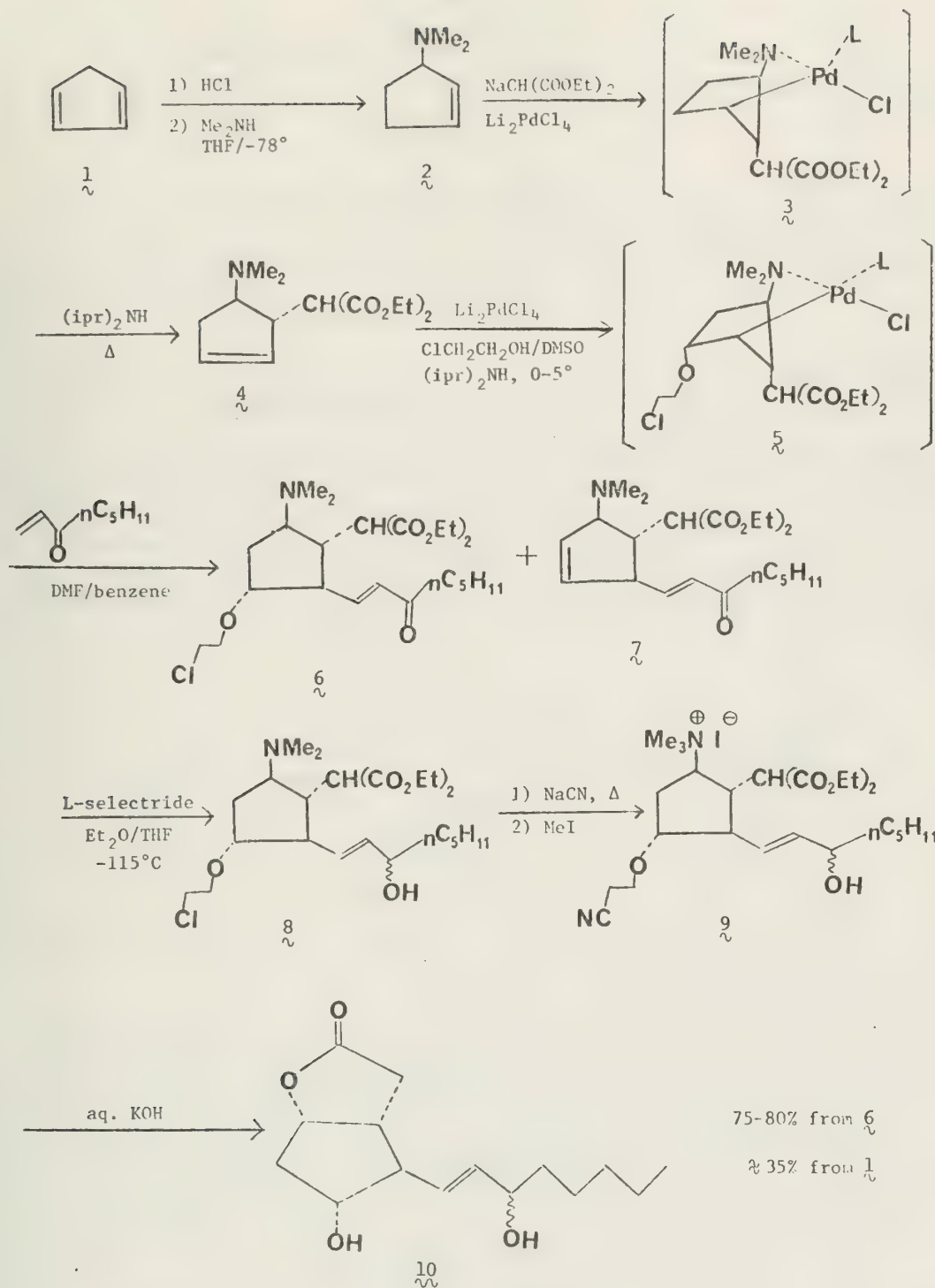


In view of the traditional difficulty of nucleophilic displacement at tertiary centers, this type of carbon-carbon bond formation is potentially an important reaction. These complexes can be easily reduced to the corresponding γ -amino or γ -alkylthio esters or ketones by sodium borohydrides in 80-96% yields. Hence, by complexing the olefin to palladium and subsequent depalladation, a carbon nucleophile has effectively been added to a double bond.

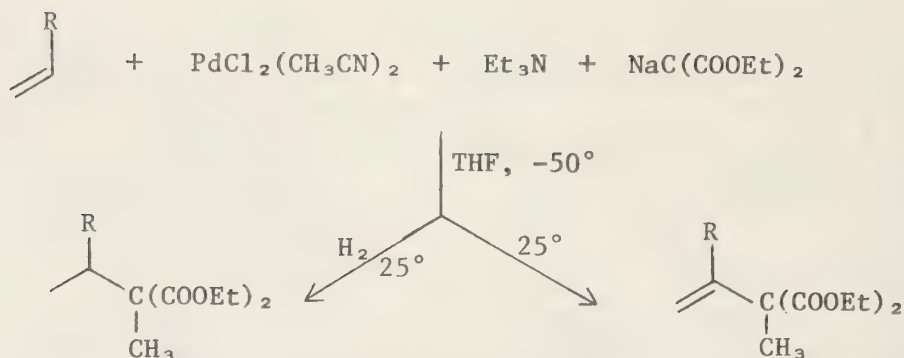
The other important reaction these complexes undergo is the replacement of palladium by carbon moieties; for example:



Synthesis of Prostaglandins by Carbopalladation. The reactions described above were used to effect a highly efficient synthesis of prostaglandins. Holton's strategy⁸ includes a method for direct attachment of two side-chain fragments R and R' to the "unactivated" double bond of an appropriately substituted cyclopentene derivative. His approach was focused on synthesis of the Corey lactone, which he visualized to result from two palladations of cyclopentadiene. Using this approach, he did succeed in a simple and efficient synthesis of the Corey lactone, which can then be converted to $\text{PGF}_{2\alpha}$ in two steps in 80% yield:

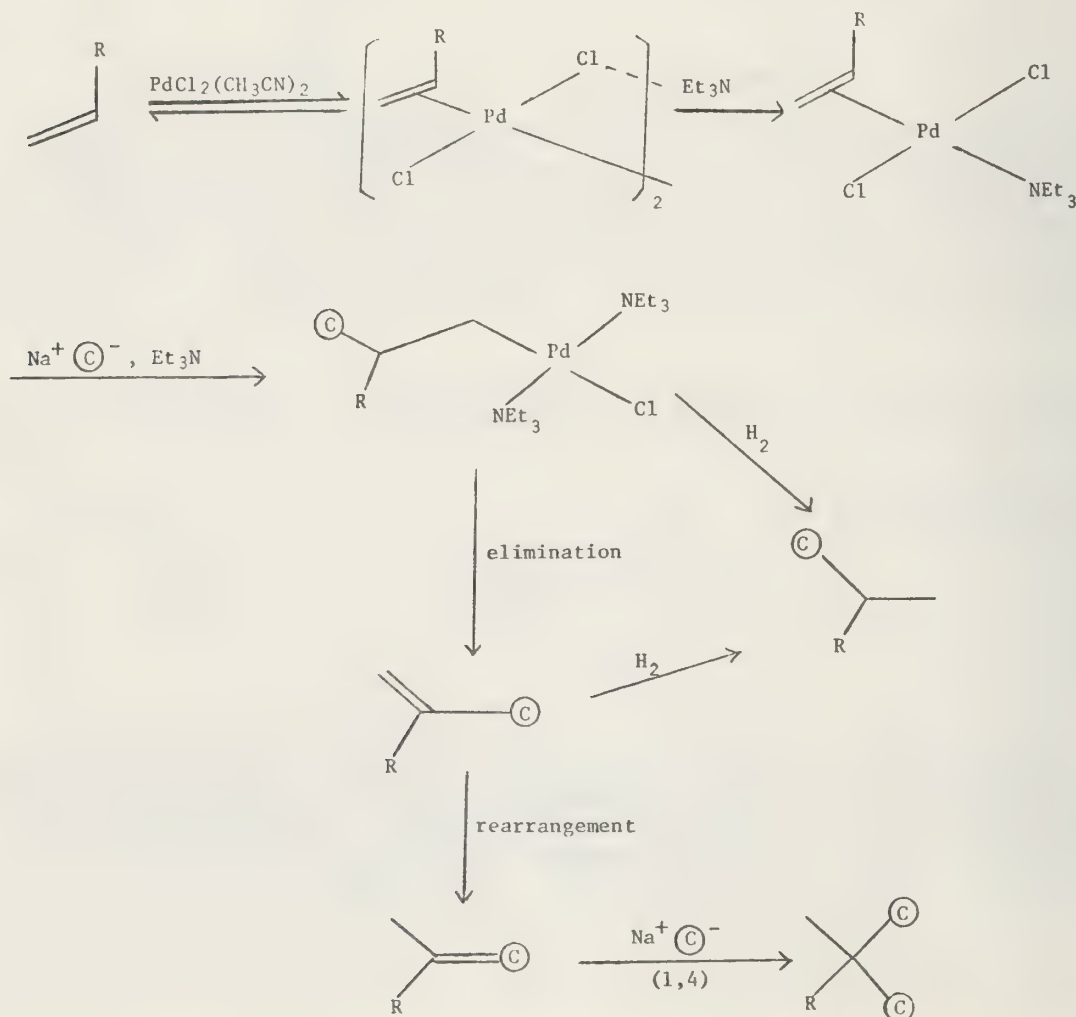


Carbopalladation of Isolated Olefins. Recently, carbopalladation of simple olefins has also been reported by Hegedus.⁹ He succeeded in the alkylation of isolated olefins by stabilized carbanions in the presence of palladium chloride and triethylamine; for example:



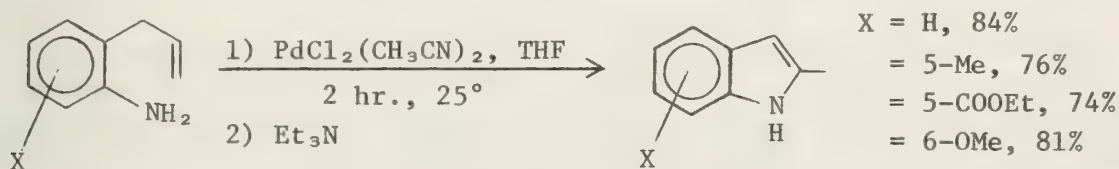
Depending on the isolation procedure, both saturated and unsaturated products could be obtained in fair-to-excellent overall yield.

In the case of substituted olefins, alkylation occurred predominantly at the most substituted position. The dialkylation products that were also observed during β -elimination isolation, with a general 10% lowering of the yield, were thought to arise from a base-catalyzed rearrangement of the initially formed olefinic product to the conjugated ester, followed by a 1,4-addition of another anion, as shown in the following scheme:

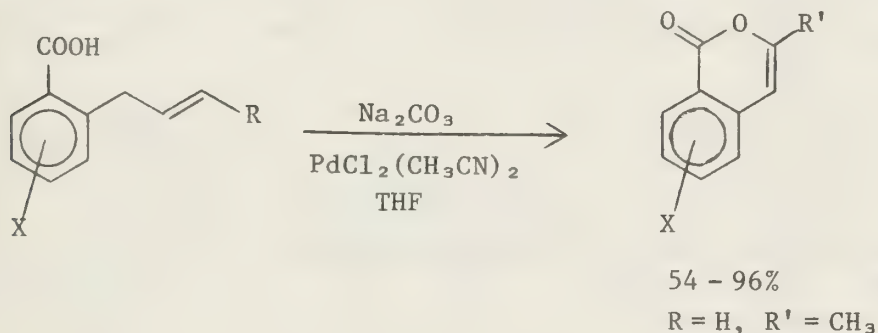


These reactions require no prior synthesis of the metal-olefin complex and no chemical removal of metal from the organic products. Rather, it is a direct "one-pot" reaction under very mild conditions. It is quite complementary to the recently reported allylic alkylations of olefin via their π -allylpalladium complexes,¹⁰⁻²¹ which lead to alkylation at the 1 and/or 3 position of the potential allyl system.

Application of Olefinic Palladations in Organic Synthesis. Work has also been done on other nucleophilic additions to olefin via palladium complexes. For example, amination has been developed as a means of cyclizing *o*-allylanilines to 2-methylindoles in high yields under remarkably mild conditions:²²



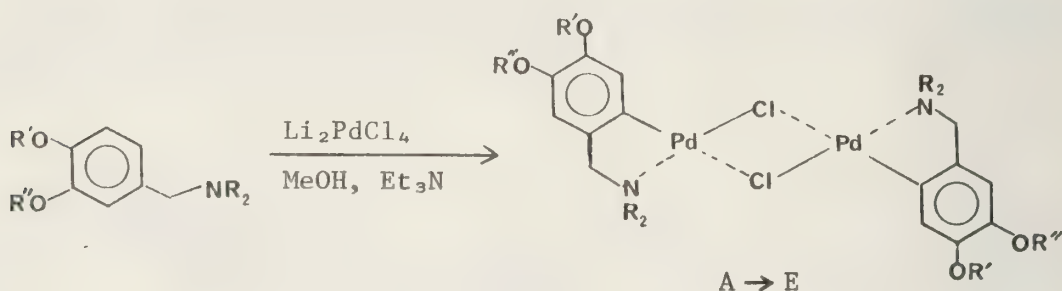
Similarly, oxygen nucleophiles have been added to olefins to obtain isocoumarins, dihydroisocoumarins and isoquinolones through palladations:²³



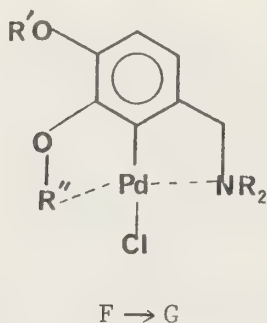
Aromatic Palladations. In 1968, Cope reported an electrophilic palladation of N,N-dimethylbenzylamine to give stable or ortho palladated complex in good yield.²⁴ This prompted Holton to develop a rational methodology to allow selective ortho coupling of 3,4-dioxygenated benzylic amines which is considered a key step in the biosynthesis of a large number of structurally diverse natural products such as oxomaritidine and narwedine.^{25,26} Holton's approach to this problem involved the regiospecific activation of 3,4-dioxygenated benzylic amines by complexing to palladium, followed by intramolecular replacement of palladium by the appropriate carbon moiety. Indeed, palladations of various dioxygenated benzylic amines by lithium tetrachloropalladate in methanol containing triethylamine did give the corresponding complexes in high yield,²⁷ as summarized in the following table:

Benzylic Amine				Complex		
No.	R	R'	R''	6-isomer %	2-isomer %	yield %
A	Et	CH ₂		100	0	98
B	Et	Me	H	100	0	95
C	Et	Me	COCH ₃	100	0	52
D	Et	Me	CH ₂ OCH ₃	100	0	85
E	Et	Me	CH ₂ Ph	100	0	58
F	Et	Me	CH ₂ SPh	0	100	42
G	Et	Me	CH ₂ SCH ₃	0	100	95

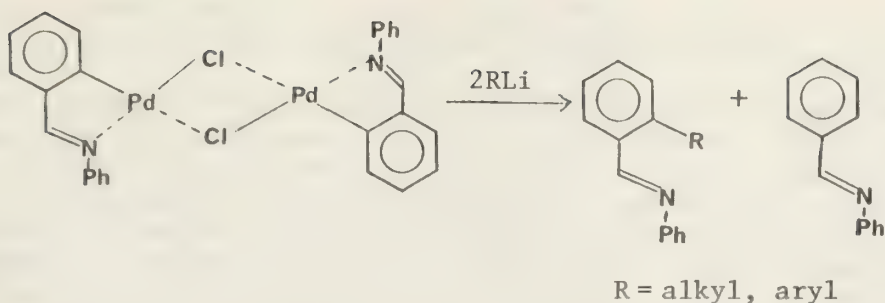
Palladation is regiospecific. For amines A-E, metallation occurred exclusively at C-6 to give dimeric complexes,



while for amines F and G, metallation occurred at C-2 to give monomeric complexes:

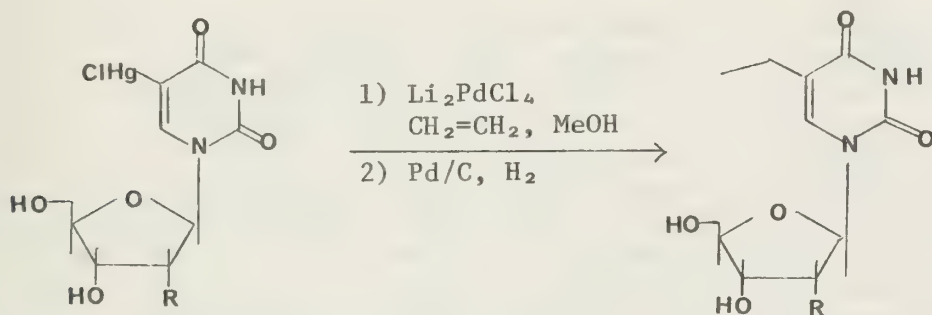


Several procedures for regiospecific replacement of palladium by carbon moieties in complexes similar to A to E have been described; these include carbonylation,²⁸ ketovinylation,²⁹ alkylation, and arylation.³⁰



Attempts are also being made to synthesize phenolic alkaloids using an intramolecular replacement of palladium by the appropriate carbon moieties in the above complexes.²⁷

Synthesis of Pyrimidine Nucleosides by Carbopalladations. Carbo-palladation has also been applied to formation of carbon-carbon bonds to unprotected nucleosides.³¹ Most syntheses of pyrimidine nucleosides with a carbon chain at C-5 have been accomplished by way of condensation between the protected, activated sugar and the C-5 substituted base. In some cases, the synthesis and purification have proven difficult.³¹ Bergstrom has recently developed a palladium-mediated alkylation of the unprotected nucleosides to form the carbon-carbon bond at C-5, hence eliminating all of the difficulties involved in condensations. For example, 5-ethyl-uridine can be synthesized from 5-chloromericuridine in two steps in 86% yield:



Conclusion. Many other organotransition metal compounds can be employed as important intermediates in organic syntheses to effect chemical conversions that could be achieved by traditional methodologies only with great difficulty.

BIBLIOGRAPHY

1. D. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
2. (a) E. J. Corey and G. N. Widiger, *J. Org. Chem.*, **40**, 2975 (1975); (b) J. Ficini and J. C. Depezay, *Bull. Soc. Chim. Fr.*, 3878 (1966); (c) J. Ficini and J. C. Pepezay, *Tetrahedron Lett.*, 4797 (1969); (d) J. C. Depezay and Y. L. Merrer, *ibid.*, 2751, 2755 (1974); (e) E. J. Corey and J. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 1851 (1969); (f) J. B. Siddal, M. Biskup, and J. Fried, *ibid.*, **91**, 1853 (1969); (g) J. P. Marino and D. M. Floyd, *ibid.*, **96**, 7138 (1974); (h) J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, 3897 (1975); (i) J. P. Marino and J. S. Farina, *ibid.*, 3901 (1975); (j) J. Ficini, G. Sarrade-Loucheur, and H. Normant, *Bull. Soc. Chim. Fr.*, 1219 (1962);

- (k) E. J. Corey, D. E. Cane, and L. Libit, *J. Am. Chem. Soc.*, 93, 7016 (1971); (l) M. Schlosser and E. Hammer, *Helv. Chim. Acta*, 57, 2547 (1974).
3. (a) D. Evans, G. C. Andrews, T. T. Fugimoto, and D. Wells, *Tetrahedron Lett.*, 1385, 1389 (1973); (b) J. F. Biellman and J. B. Ducep, *ibid.*, 5629 (1968); (c) E. J. Corey, B. W. Erikson, and R. Noyori, *J. Am. Chem. Soc.*, 93, 1724 (1971); (d) K. Oshima, H. Takahashi, H. Yamamoto, and H. Nozaki, *ibid.*, 95, 2693 (1973); (e) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, 95, 4446 (1973); (f) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, 95, 5803 (1973); (g) P. L. Stotter and R. E. Hornish, *ibid.*, 97, 4444 (1974); (h) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, 95, 7926 (1973); (i) S. Torli, H. Tanaka, and Y. Tomotaki, *Chem. Lett.*, 1541 (1974); (j) P. M. Atlani, J. F. Biellmann, S. Dube, and J. J. Vicens, *Tetrahedron Lett.*, 2665 (1974); (k) T. Taguchi, H. Okamura, and H. Takei, *Chem. Lett.*, 853 (1975); (l) T. Cohen, D. Bennett, and A. J. Mura, *J. Org. Chem.*, 41, 2506 (1976); (m) R. Kow and M. W. Rathke, *J. Am. Chem. Soc.*, 95, 2715 (1973).
4. (a) D. A. Evans and G. C. Andrews, *J. Am. Chem. Soc.*, 96, 5560 (1974); (b) W. C. Still and T. L. Macdonald, *ibid.*, 96, 5561 (1974); (c) W. C. Still and T. L. Macdonald, *J. Org. Chem.*, 41, 3620 (1976); (d) W. C. Still, *Tetrahedron Lett.*, 2115 (1976); (e) H. Ahlbrecht and G. Rauchschalbe, *Synthesis*, 417 (1973); (f) H. Ahlbrecht and J. Eichler, *ibid.*, 672 (1974); (g) M. Julia, A. Schouteeten, and M. Ballarge, *Tetrahedron Lett.*, 3433 (1974).
5. R. A. Holton, *J. Am. Chem. Soc.*, 99, 4177 (1977).
6. H. Takahashi and J. Tsuji, *ibid.*, 90, 2387 (1968).
7. B. F. G. Johnson, J. Lewis, and M. S. Subramanian, *J. Chem. Soc. A*, 1993 (1968).
8. R. A. Holton, *J. Am. Chem. Soc.*, 99, 8083 (1977).
9. T. Hayashi and L. S. Hegedus, *ibid.*, 99, 7093 (1977).
10. B. M. Trost and T. J. Fullerton, *ibid.*, 95, 292 (1973).
11. B. M. Trost and T. J. Dietsch, *ibid.*, 95, 8200 (1973).
12. B. M. Trost and L. Weber, *ibid.*, 97, 1611 (1975).
13. B. M. Trost and P. Strege, *ibid.*, 97, 2534 (1975).
14. B. M. Trost and L. Weber, *J. Org. Chem.*, 40, 3617 (1975).
15. B. M. Trost, W. P. Conway, P. E. Strege, and T. J. Dietsche, *J. Am. Chem. Soc.*, 96, 7165 (1974).
16. B. M. Trost and T. R. Verhoeven, *ibid.*, 98, 630 (1976).
17. B. M. Trost and T. R. Verhoeven, *ibid.*, 98, 631 (1976).
18. B. M. Trost and P. E. Strege, *ibid.*, 99, 1649 (1977).
19. B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, 41, 2750 (1976).
20. W. R. Jackson and J. U. B. Strauss, *Tetrahedron Lett.*, 2591 (1975).
21. D. J. Collins, W. R. Jackson, and R. N. Timms, *ibid.*, 495 (1976).
22. L. S. Hegedus, G. F. Allen, and E. L. Waterman, *J. Am. Chem. Soc.*, 98, 2674 (1976).
23. D. E. Korte, L. S. Hegedus, and R. K. Wirth, *J. Org. Chem.*, 42, 1329 (1977).
24. A. C. Cope and E. C. Fredrich, *J. Am. Chem. Soc.*, 90, 909 (1968).
25. D. H. R. Barton and T. Cohen, "Festschrift A. Stoll", Birkhauser, Basel, 1957, p. 117.
26. J. M. Paton, P. L. Pauson, and T. S. Stevens, *J. Chem. Soc. C*, 1309 (1975).
27. R. A. Holton and R. G. Davis, *J. Am. Chem. Soc.*, 99, 4175 (1977).
28. J. M. Thompson and R. F. Heck, *J. Org. Chem.*, 40, 2667 (1975).
29. R. A. Holton, *Tetrahedron Lett.*, 355 (1977).
30. S. Murahashi, Y. Tanaba, M. Yamamura, and I. Moritani, *ibid.*, 3749 (1974).

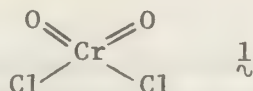
31. D. E. Bergstrom and J. L. Ruth, ibid., 98, 1587 (1976).
32. A. C. Cope, J. M. Kliegman, and E. C. Friedrich, ibid., 89, 287 (1967).
33. Y. Takahashi, A. Tokuda, S. Sakai, and Y. Ishii, J. Organometal. Chem., 35, 415 (1972).

THE MECHANISM OF THE CHROMYL CHLORIDE REACTION WITH OLEFINS

Reported by Raul Oteiza

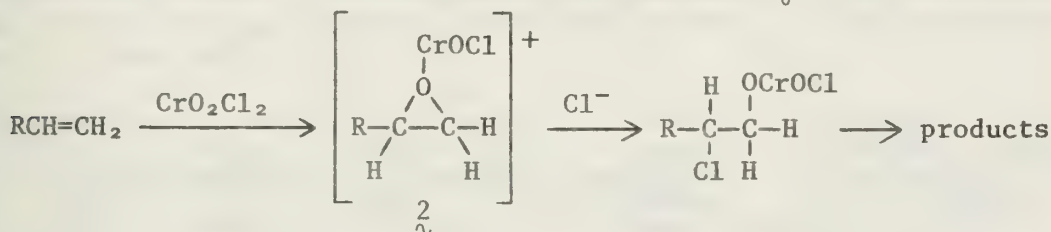
April 24, 1978

Chromyl chloride, $\overset{1}{\underset{\sim}{\text{CrO}_2\text{Cl}_2}}$, was introduced as a means of converting carbon-carbon double bonds to ketones or aldehydes. It was hoped that it might



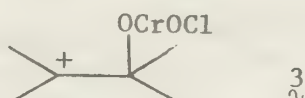
become the most useful and versatile of the readily available chromium (VI) oxidizing agents. Although ketones and aldehydes can be produced under controlled conditions, these oxidations have been found to produce complex mixtures of products.¹⁻¹⁰ Since most studies of olefin oxidation have dealt primarily with the composition of the product mixtures, controversy exists concerning the mechanism of the reaction. Not until recently has the reaction been carefully investigated and a more reasonable reaction scheme been postulated.

The mechanism of chromyl chloride oxidation of olefins was initially suggested¹ to involve electrophilic attack by a species such as $[\text{CrO}_2\text{Cl}]^+$ on the olefin to give a three-centered intermediate $\overset{2}{\underset{\sim}{}}$. The intermediate

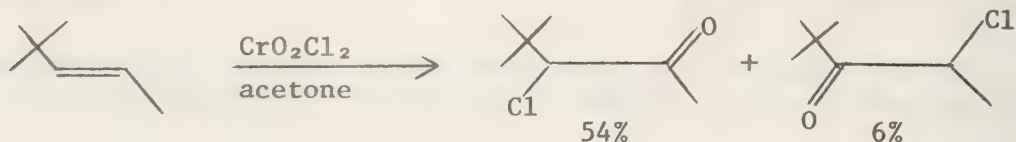


would then be attacked from the backside by chloride ion to produce a chlorohydrin precursor. The scheme was based on the observations that the oxidation of cyclohexene gave the trans chlorohydrin and terminal olefins yielded products corresponding to anti-Markovnikoff addition of the elements of HOCl . Several years later, Sulima and Gragerov¹¹ found by way of ^{18}O tracer studies that all of the oxygen in the chlorohydrin was due to chromyl chloride. Thus, they corroborated the idea that the chromyl chloride had to attach itself to the olefin to form a one-to-one adduct. The nature of the adduct was not proposed in this later work.

The work of Stairs and his co-workers² later complicated the mechanistic scheme. These workers, in studying the oxidation of cyclohexene and cyclopentene, were able to isolate as major products both the cis and trans chlorohydrins. Since both geometric isomers were being formed, they concluded that the cyclic oxonium intermediate could not provide the only route to products. To explain their observations, they proposed electrophilic attack by chromyl chloride to form a free carbonium ion intermediate $\overset{3}{\underset{\sim}{}}$. The ratio of the products would then be due to



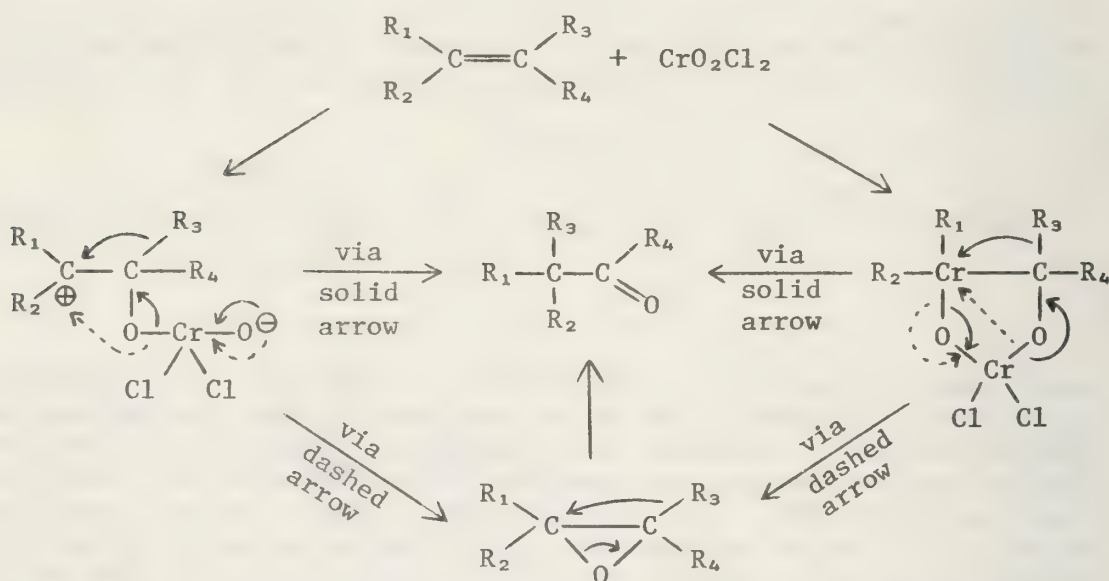
thermodynamic control. This view of the mechanism has more recently been refuted.¹⁰ A study of the oxidation of (E)-t-butylmethylethylene with chromyl chloride produced only the corresponding chloro ketones. No



products due to Wagner-Meerwein rearrangements were observed. This result argues against significant cationic character in the step in which the carbon-chlorine bond is formed.

In the late 1960's, Freeman and his co-workers began to investigate the chromyl chloride oxidations. Under the reaction conditions they applied, they found the major product to consist of ketones resulting from alkyl group rearrangement. In an early communication³ they proposed the routes shown in Scheme I.

Scheme I

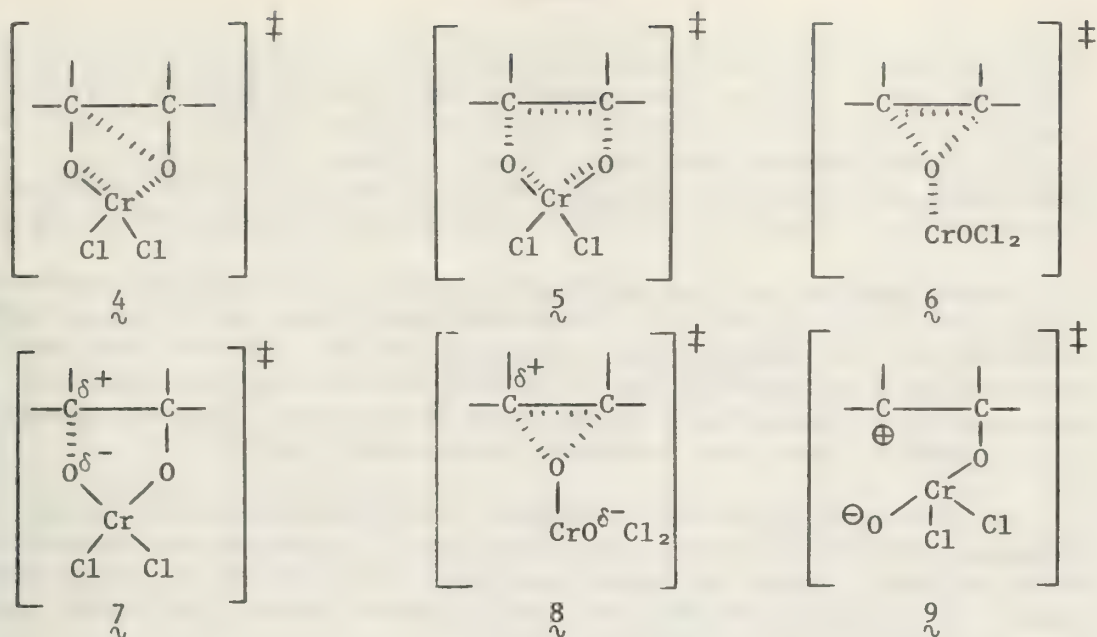


Beginning with the premise of electrophilic addition by the chromyl chloride oxygen on the olefin, Freeman set out to do kinetic and mechanistic investigations. His work revolved about the assumption that the transition state had to resemble one of structures 4-9.⁵ He then proceeded to carry out investigations to exclude all but one of these transition states.⁵⁻⁷

Stop-flow kinetic studies were able to show that the reaction was smoothly first order in both substrate and oxidizing agent. Thus, the rate of the reaction followed the second order expression:

$$\frac{-d(\text{CrO}_2\text{Cl}_2)}{dt} = k[\text{alkene}][\text{CrO}_2\text{Cl}_2]$$

Following the kinetics at various temperatures afforded an Arrhenius plot from which thermodynamic parameters could be obtained. Depending on the

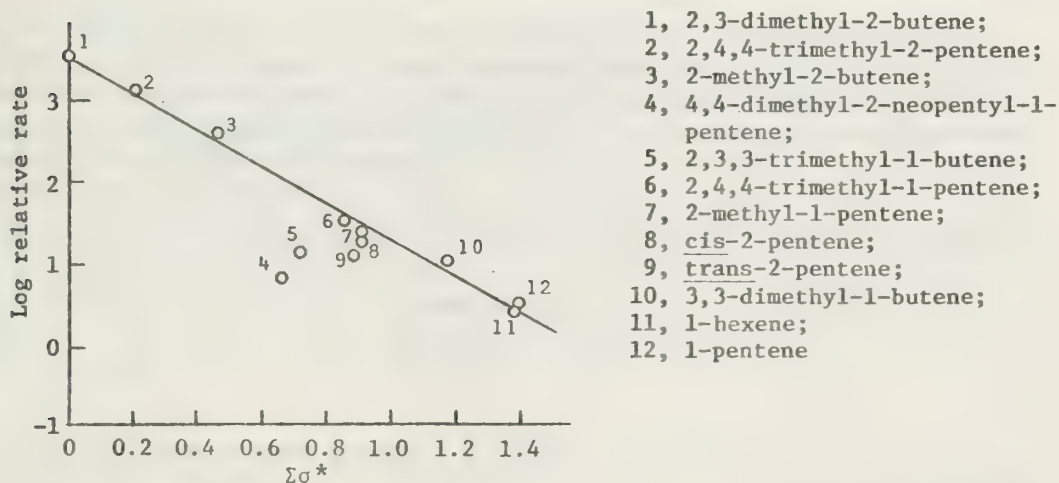


olefin under investigation, ΔH^\ddagger ranged from 2 to 10 Kcal/mole and ΔS^\ddagger ranged from -23 to -43 e.u. Thus, he concluded that the reaction was bimolecular and had a very highly ordered transition state. By comparison, to the enthalpy and entropy of activation of such reactions as epoxidation and bromination, he postulated that the transition state was most likely three-centered in nature. This supported structures $\tilde{6}$ and $\tilde{8}$ as possible transition states.

Dissolved oxygen had no effect on the reaction rate, thus showing that the reaction was not free radical in nature. The relative reaction rates in four different solvents indicated that the transition state was polar in nature since increases in solvent polarity increased the rate of disappearance of chromyl chloride.

On the assumption of simple additivity of substituent effects and with neglect of interaction terms, a linear correlation with log relative rate vs. Taft's inductive σ^* substituent constants was obtained, as seen in Figure 1.

Figure 1

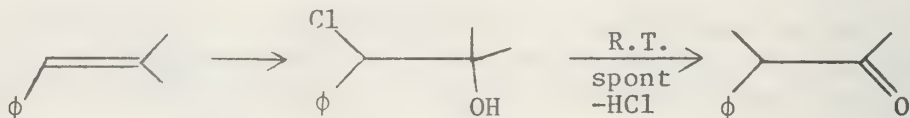


This indicated that the transition state was cationic in nature; however, the ρ value of -2.6 was less negative than those generally observed for reactions involving a fully developed carbonium ion in the transition state. These observations supported structures 7 and 8 for the transition state and discounted 4, 5, 6 and 9, 9 having a fully developed carbonium ion, 5 being concerted in nature, and 4 and 6 not being polar.

Using styrene as his substrate, Freeman investigated secondary deuterium isotope effects.⁶ For α -deuteriostyrene, he observed $k_H/k_D = 0.98$ and for β,β -dideuteriostyrene, $k_H/k_D = 0.88$. To him, this was in accord with a mechanism in which initial attack occurred at the β carbon with a concomitant development of a partial positive charge at the α carbon. This also supported structures 7 and 8.

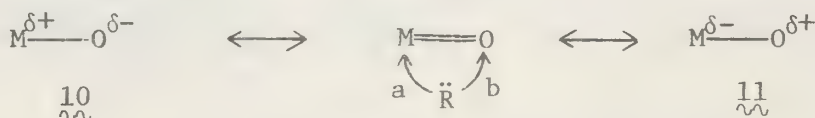
As the deciding study, a complex relationship between strain energies and rate constants was developed. This relation suggested that no significant amount of strain was being relieved in the transition state. It was this observation that prompted Freeman to choose structure 8 as the most likely transition state.

The following year Bachelor⁸ refuted Freeman's work. Bachelor claimed that in all the investigations Freeman had performed, he had never stated his reaction and work-up conditions. Bachelor also stated that when he attempted to repeat Freeman's work using norbornene as substrate, he obtained the exo-cis-chlorohydrin as the major (74%) product. He maintained that Freeman's mechanism and results were inconsistent with what he observed, since no rearrangement was seen to occur with norbornene and since cis addition could not arise from Freeman's oxonium intermediate. Yet, there is a flaw in Bachelor's experiment since norbornene is well known for its unusual preference for cis additions.¹² But Freeman's mechanism can still be disclaimed on Bachelor's first argument. More recently, it has been shown¹⁰ that when the chlorohydrin Freeman would have obtained is allowed to stand at room temperature, it spontaneously



rearranges. This accounts for Freeman's observations and adds support to the unsuitability of his mechanism.

About this same time Sharpless and his co-workers began to study several metal oxo compounds, among these, chromyl chloride. He reconsidered the original premise for the reaction and felt there was something inherently wrong with it. The mechanism had always been regarded as electrophilic in nature, but the initiating step had always been attack of the oxygen atom on the olefin, path b. This implied that the polarization of the metal-oxo bond is as shown in 11. Besides being contrary



to common sense, this is contrary to dipole moment studies,^{13,14} ab initio calculations,^{15,16} and photoelectron studies¹⁷ which all show that

the metal-oxo bond has the dipolar structure ¹⁰. Thus, a more likely path would be that shown in a, and this led Sharpless into detailed studies on the chromyl chloride mechanism.

In an early study¹⁸ his group found that when these oxidations were carried out at low temperatures, the epoxide and the chlorohydrin were the major products (Table 1).

Table 1. CrO₂Cl₂ Oxidations of Disubstituted Olefins

Olefin	Epoxide		Halohydrin		Halo ketone
	Z	E	Erythro	Threo	
1. (E)-Cyclododecene	2	20	5	60	8
2. (Z)-Cyclododecene	28	2	25	4	5
3. (E)-5-Decene	1	15	5	55	7
4. (Z)-5-Decene	13	2	35	30	5
5. Cyclohexene	5		15	25	5

More important, the chlorohydrin resulted from stereoselective cis addition across the olefinic linkage. These observations were also supported by other groups who had previously obtained epoxides¹⁹ and cis-chlorohydrins⁸ as their major products.

Since some trans addition was noted, careful control experiments were performed.²⁰ The results are shown in Table 2. Entries 1 and 2 show that epoxides are stable to the reagent itself. Entries 3-6 show

Table 2

Compound	Condi- tions ^a	Epoxides		Chlorohydrins		Chloro ketone
		Z	E	Erythro	Threo	
1. (E)-Cyclododecene oxide	I		100			
2. (Z)-Cyclododecene oxide	I		100			
3. (E)-Cyclododecene oxide	II		85	15		
4. (Z)-Cyclododecene oxide	II		82		15	
5. (E)-5-Decene oxide	III	2	55	35	3	5
6. (Z)-5-Decene oxide	III	27	3		43	4
7. <u>erythro</u> -2-Chlorocyclo- dodecanol	II			100		

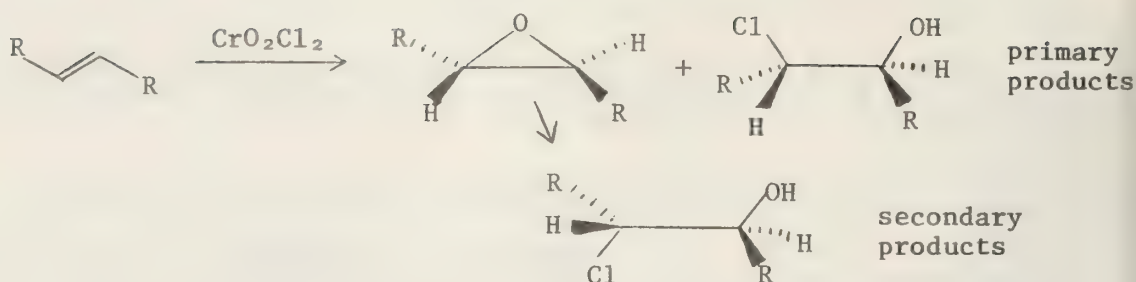
^aI: The epoxide and 1 equiv of CrO₂Cl₂ were stirred at -78°C for 2 h.

II: The oxidation of (E)-5-decene was carried out in the presence of 1 equiv of the compound to be tested.

III: The oxidation of (E)-cyclododecene was carried out in the presence of 1 equiv of the compound to be tested.

that under reaction conditions the epoxides undergo trans opening. Entry 7 shows that the chlorohydrins are stable under reaction conditions. These facts lead to the conclusion that the trans chlorohydrins must be secondary products arising from the opening of the epoxide in the reaction mixture (Scheme II).

Scheme II



Further studies²⁰ were performed in order to verify these results. The olefin (E)-1-deuterio-1-decene was oxidized by chromyl chloride and the products were analyzed. The results are shown in Table 3. Table 4 shows

Table 3. CrO_2Cl_2 Oxidation of (E)-1-Deuterio-1-decene

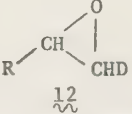
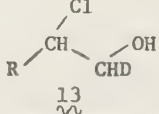
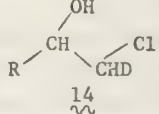
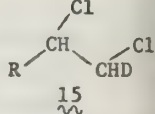
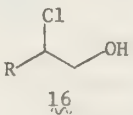
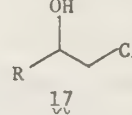
Solvent (temp, time)	% yields (threo:erythro)			
	 12	 13	 14	 15
1. CH_2Cl_2 (-78°C , 3 h)	3(>98:2)	26(86:14)	6(58:42)	12(>98:2)
2. CCl_4 (0°C , 1 h)	3(>98:2)	34(85:15)	12(67:33)	2(>98:2)

Table 4. Control Experiment for 1-Decene Oxidations^a

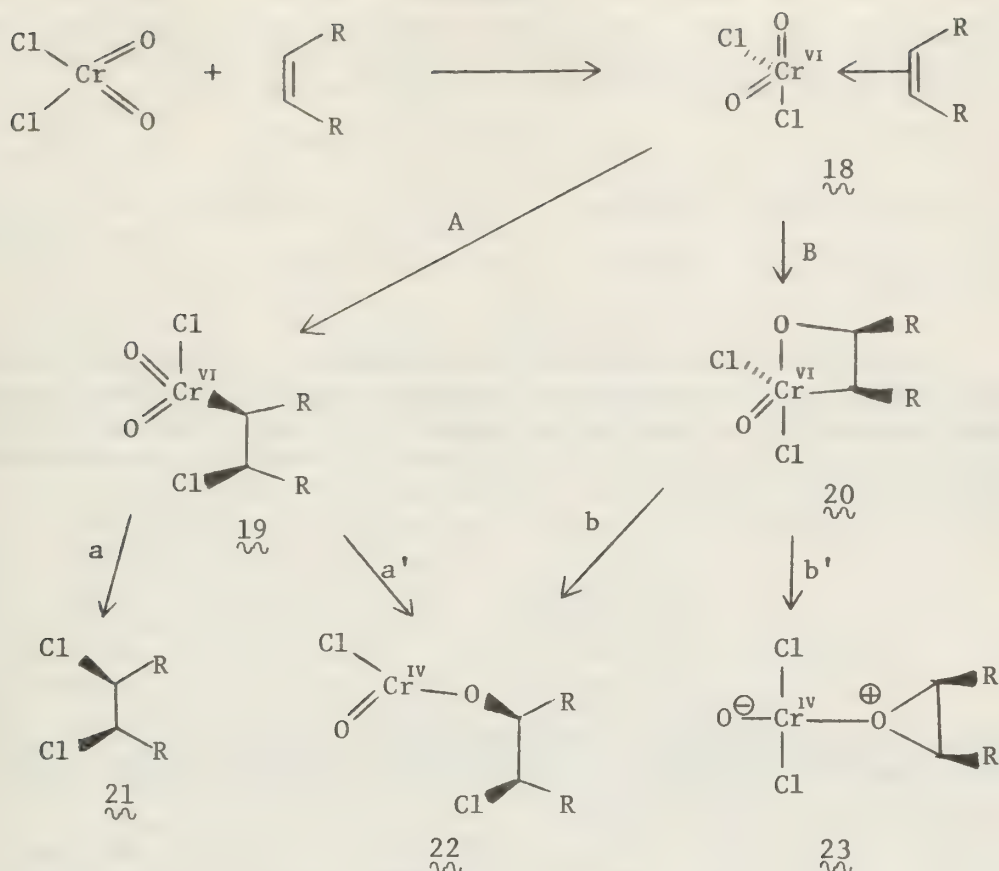
	% yields		
	Recovered oxide	 16	 17
1-Decene oxide	10	26	19
(1.4:1)			

^aThe CrO_2Cl_2 oxidation of 1-hexene was carried out at 0°C in CCl_4 in the presence of 0.1 equiv of 1-decene oxide.

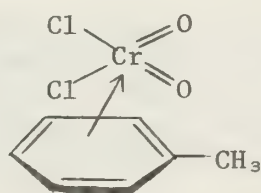
the results of the control experiment. This experiment was performed to determine the amount and direction of epoxide opening. The results indicated that under conditions designed to simulate those of the oxidation 1-decene oxide opens to a 1.4:1 ratio of chlorohydrins 16 and 17. From entry 2 in Table 3, one sees that the erythro chlorohydrins 13 and 14 have been formed in a ratio of 1.3:1. Thus, the erythro chlorohydrins in Table 3 arise from trans opening of the (E)-epoxide. Again, the products are seen to be formed from highly stereoselective cis addition, which conforms with Scheme II.

These observations were not readily explained by the previously proposed mechanisms¹⁻⁹ so Sharpless proposed an indirect route as shown in Scheme III. The first step of the proposed scheme was suggested to be the formation of a chromyl chloride-olefin π -complex. Transition metal π -complexes are known in organometallic chemistry, and palladium or

Scheme III



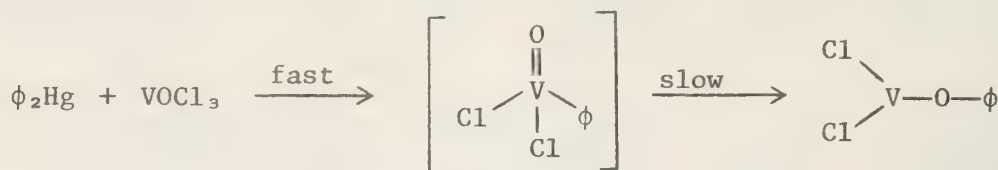
platinum-olefin π -complexes are well known in organic reduction reactions, although in these complexes the transition metal is in a low valence state. A similar type of complex was previously postulated by Stairs²¹ in the reaction of chromyl chloride with aryl groups, the Étard reaction:



Since the transition state **18** is a high valent d^0 transition metal coordination complex, Sharpless believed that olefin insertion was likely to occur. Two possible paths were available, insertion into a σ bond, path A, or into a π bond, path B, both of which lead to chromium(VI) organometallic intermediates.

In path A, the olefin inserts into a chromium chlorine bond (cis chlorometalation) to produce an alkyl chromium intermediate, **19**. This could lead to the dichloride **21** by reductive elimination, **a**, or to the chromium derivative of the chlorohydrin **22** by migration of the alkyl group from chromium to oxygen, **a'**. A complex of tungsten very similar to **19**, $\text{CH}_3\text{WO}_2\text{Cl}$, has been characterized,²² thus lending some support to this intermediate. In order for the products to show the correct stereochemistry, both processes would have to occur with retention of configuration in order to result in overall cis addition. Reductive eliminations to form a carbon-halogen bond, **a**, are known in organometallic chemistry

and proceed via retention at carbon.²³⁻²⁵ The 1,2 migration shown in a' might be expected to occur with retention at carbon by analogy with a Stevens type of rearrangement.²⁶ A precedent for such a rearrangement has been reported²⁷ for the phenyl oxovanadium species:



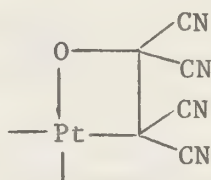
In path B a four-centered intermediate, 20, is formed via what is formally a 2+2 interaction of the olefin and an oxo group of chromium. This process can be seen to be essentially the microscopic reverse of the olefin-forming step in the Wittig reaction where the oxyphosphetane decom-



poses to the phosphine oxide and an olefin.²⁸ Also, recently SO_3 has been shown²⁹ to undergo stereospecific 2+2 cis addition to (E)- and (Z)-



2-butene to give the corresponding β -sultones. A platinum metallo-cycle with the same structural features as 20 has also been characterized.³⁰



Intermediate 20 can now be seen to yield the chlorohydrin precursor, b, or the epoxide precursor, b', by the appropriate reductive elimination.

Sharpless considers that paths A and B are competing processes and that the extent of involvement of each varies with the nature of the substrate and reaction conditions. To verify this is his current goal.

Although the Sharpless mechanism is not conclusive, it does account for the observed data better than the earlier mechanisms. By inspection it can be seen that this mechanism can also explain the data obtained by Freeman, thus rendering them acceptable. The Sharpless mechanistic scheme provides a fresh alternative and a focus for new thought and experimentation.

BIBLIOGRAPHY

1. S. J. Cristol and K. R. Eilar, J. Am. Chem. Soc., 72, 4353 (1950).
2. R. A. Stairs, D. G. M. Diaper, and A. L. Gatzke, Can. J. Chem., 41, 1059 (1963).
3. F. Freeman, P. J. Cameron, and R. H. DuBois, J. Org. Chem., 33, 3970 (1968).
4. F. Freeman, R. H. DuBois, and N. J. Yamachika, Tetrahedron, 25, 3441 (1968).
5. F. Freeman, P. D. McCart, and N. J. Yamachika, J. Am. Chem. Soc., 92, 4621 (1970).
6. F. Freeman and N. J. Yamachika, *ibid.*, 94, 1214 (1972).
7. F. Freeman and K. W. Arledge, J. Org. Chem., 37, 2656 (1972).
8. F. W. Bachelor and U. O. Cheriyan, Tetrahedron Lett., 3291 (1973).
9. K. B. Wiberg, "Oxidation in Organic Chemistry", Part A, Academic Press, New York, 1965.
10. K. B. Sharpless and A. Y. Teranishi, J. Org. Chem., 38, 185 (1972).
11. L. V. Sulima and I. P. Gragerov, J. Gen. Chem. USSR (Engl. Transl.), 3787 (1959).
12. T. G. Traylor, Acc. Chem. Res., 2, 152 (1969).
13. H. Takea and H. Hirola, J. Mol. Spectrosc., 41, 420 (1972).
14. F. W. Moore and R. E. Rice, Inorg. Chem., 7, 2510 (1968).
15. H. Johansen, Chem. Phys. Lett., 17, 569 (1972).
16. P. D. Dacre and M. Elder, *ibid.*, 11, 377 (1971).
17. P. Burroughs, S. Evans, A. Hammett, A. F. Orchard, and N. V. Richardson, J. Chem. Soc., Faraday Trans., 2, 70, 1895 (1974).
18. ref. 12 in K. B. Sharpless, A. Y. Teranishi, and J.-E. Bäckvall, J. Am. Chem. Soc., 99, 3120 (1977).
19. F. W. Bachelor and U. O. Cheriyan, J. Chem. Soc., Chem. Commun., 195 (1973).
20. K. B. Sharpless, A. Y. Teranishi, and J.-E. Bäckvall, J. Am. Chem. Soc., 99, 3120 (1977).
21. R. A. Stairs, Can. J. Chem., 42, 550 (1964).
22. C. Santini-Scampussi and J. G. Riess, J. Organometal. Chem., 73, C13 (1974).
23. D. R. Coulson, J. Am. Chem. Soc., 91, 200 (1969).
24. R. W. Johnson and R. G. Pearson, Chem. Commun., 986 (1970).
25. R. G. Pearson and W. R. Muir, J. Am. Chem. Soc., 92, 5519 (1970).
26. A. R. Lepley and A. G. Guimanini in "Mechanisms of Molecular Migrations", Vol. 3, B. S. Thayagarajan, ed., Wiley-Interscience, New York, 1971, pp. 297-440.
27. W. J. Reichle and W. L. Carrick, J. Organometal. Chem., 24, 419 (1970).
28. E. Vedejs and K. A. J. Snoble, J. Am. Chem. Soc., 95, 5778 (1973).
29. M. Nagayama, O. Okumura, S. Noda, and A. Mori, J. Chem. Soc., Chem. Commun., 841 (1973).
30. R. Schlodder, J. A. Ibers, M. Lenarda, and M. Graziani, J. Am. Chem. Soc., 96, 6893 (1974).

CHEMICALLY INITIATED ELECTRON EXCHANGE LUMINESCENCE

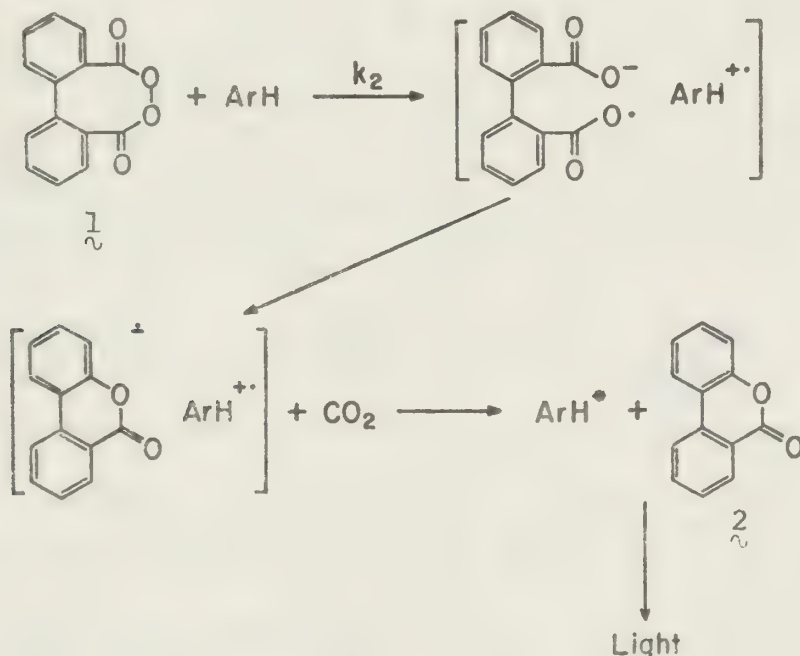
Reported by Steven P. Schmidt

April 27, 1978

Two general mechanistic schemes for chemiexcitation have emerged from previous studies of chemiluminescence in solution. The first, exemplified by the well studied 1,2-dioxetane system,¹ involves thermal rearrangement of a high energy reactant to generate an electronically excited state of a product molecule.² The second mechanism, known as electrogenerated chemiluminescence (ECL),³ involves no change in chemical bonding. In this scheme, a radical cation and radical anion form a diffusive encounter pair and mutually annihilate, generating an electronically excited state.

Recently, a new mechanism for efficient chemiluminescence, identified as chemically initiated electron exchange luminescence (CIEEL), has been advanced.^{4a} This model, which incorporates certain aspects of each of the two conventional chemiexcitation models, appears to explain chemical light formation in many important systems and provide a ready rationalization for many previously perplexing observations of chemi- and bioluminescence.

The CIEEL pathway has been most thoroughly investigated with diphenoyl peroxide (1).⁴ Unimolecular decomposition of 1 to benzocoumarin (2) occurs without significant generation of excited states. Addition of an easily oxidized aromatic hydrocarbon, however, leads to efficient chemiexcitation of the hydrocarbon. Most significantly, various aromatic hydrocarbons catalyze the decomposition of 1 , with a rate which correlates with their one-electron oxidation potential. Thus, the initiating step of the catalytic, light-generating path is an activated electron transfer from the hydrocarbon to the peroxide. Subsequent decarboxylation, closure to the radical anion of benzocoumarin, and charge annihilation generates an electronically excited state of the hydrocarbon. Exciplex emission, solvent effects, and independent generation of intermediates further support the suggested reaction sequence.



It had been reported some time ago that the addition of certain aromatic hydrocarbons to solutions of dimethyldioxetanone led to hydrocarbon luminescence and markedly increased the light yield.⁵ Further investigation of reaction kinetics and the efficiency of light production as a function of added hydrocarbon revealed CIEEL to be the major light generating path from dimethyldioxetanone under these conditions.⁶ Similarly, Sawaki and Ogata have suggested a chemiluminescence mechanism involving a charge transfer complex between dioxetanones, postulated intermediates in the base catalyzed decomposition of α -hydroperoxy esters, and added fluorescers.⁷

A third example of the CIEEL process is the chemiluminescent reaction of diphenyl-*o*-xylylene peroxide.⁸ In this case the initial electron transfer to the peroxide and subsequent ring opening directly generates the final radical ion pair, without an intermediate fragmentation.

Dioxetanes substituted with easily oxidized groups are remarkably different from their alkyl substituted counterparts, in that they are of low stability and afford unusually high yields of singlet excited carbonyl-containing products. Examples include the 9,10-dihydroacridan-substituted dioxetanes of Singer⁹ and McCapra¹⁰ and the anthryl-¹¹ and N,N-dimethyl-*p*-aminophenyl-¹² substituted dioxetanes of Schaap. Application of an intramolecular CIEEL process to these systems provides an explanation consistent with the experimental data.

In nearly all bioluminescent processes investigated thus far, cyclic peroxides have been implicated as key reactive intermediates.¹³ In particular, a dioxetanone has been shown to be involved in the light generating step of firefly bioluminescence.¹⁴ Application of an intramolecular CIEEL process to this system may explain the remarkably high singlet yield and the effect of structural variation.¹⁵

BIBLIOGRAPHY

1. T. Wilson, *Int. Rev. Sci.: Phys. Chem.*, Ser. 2, 9, 265 (1976).
2. F. McCapra, *Prog. Org. Chem.*, 8, 231 (1973).
3. L. R. Faulkner, *Int. Rev. Sci.: Phys. Chem.*, Ser. 2, 9, 213 (1976).
4. (a) J.-y. Koo and G. B. Schuster, *J. Am. Chem. Soc.*, 99, 6107 (1977); (b) J.-y. Koo and G. B. Schuster, *ibid.*, in press.
5. W. Adam, G. A. Simpson, and F. Yany, *J. Phys. Chem.*, 78, 2559 (1974).
6. S. P. Schmidt and G. B. Schuster, *J. Am. Chem. Soc.*, 100, 1966 (1978).
7. Y. Sawaki and Y. Ogata, *J. Org. Chem.*, 42, 40 (1977).
8. J. P. Smith and G. B. Schuster, *J. Am. Chem. Soc.*, 100, 0000 (1978).
9. K.-W. Lee, L. A. Singer, and K. D. Legg, *J. Org. Chem.*, 41, 2685 (1976).
10. (a) F. McCapra, I. Beheshti, A. Burford, R. A. Hann, and K. A. Zaklika, *J. Chem. Soc., Chem. Commun.*, 944 (1977); (b) F. McCapra, *ibid.*, 946 (1977).
11. K. A. Zaklika, P. A. Burns, and A. P. Schaap, *J. Am. Chem. Soc.*, 100, 318 (1978).
12. A. P. Schaap, abstracts of the 174th National Meeting of the American Chemical Society, Chicago, Illinois, August 1977.
13. (a) F. McCapra, *Acc. Chem. Res.*, 9, 201 (1976); (b) W. Adam, *J. Chem. Ed.*, 52, 138 (1975).
14. (a) O. Shimomura, T. Goto, and F. H. Johnson, *Proc. Natl. Acad. Sci. USA*, 74, 2799 (1977); (b) E. H. White, J. D. Miano, and M. Umbreit, *J. Am. Chem. Soc.*, 97, 198 (1975).

15. J.-y. Koo, S. P. Schmidt, and G. B. Schuster, Proc. Natl. Acad. Sci. USA, 75, 30 (1978).

SOME USES OF THALLIUM IN ORGANIC SYNTHESIS

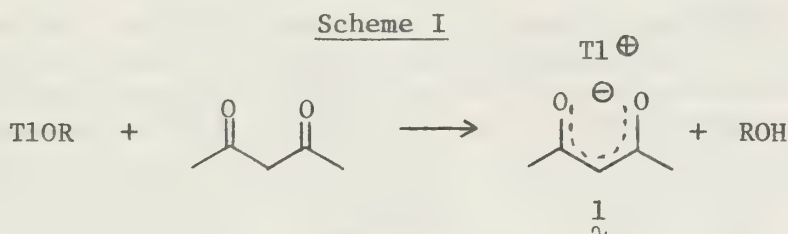
Reported by Stephen M. Ramsey

May 4, 1978

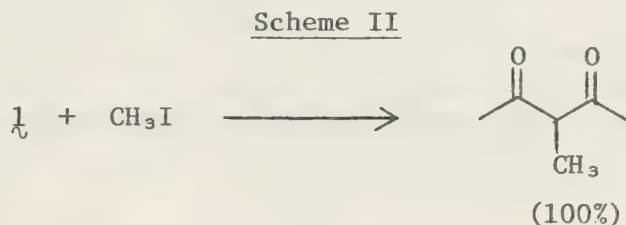
The organometallic chemistry of thallium had not been developed extensively until the 1960's. A. McKillop and E. C. Taylor have contributed most to the recent interest in the chemistry of thallium, with their development of methods for selective acylation and alkylation reactions, olefin oxidations (oxythallations), and selective aromatic substitution reactions.¹

Thallium, discovered in 1861 by Sir William Crookes, is a soft white metal oxidized slowly by air at room temperature. It is prepared commercially as a by-product from the smelting of zinc and lead ores. Thallium is a group III-A metal possessing stable 1+ and 3+ oxidation states. Inorganic thallium salts are generally more stable in the lower oxidation state, while organothallium compounds are usually stable only in the higher state. Carbon-thallium bonds are weak (~ 25 kcal/mole); they are formed easily and are very reactive. Stable organothallium derivatives can be isolated, but cleavage of the carbon-Tl(III) bond is extremely facile and allows easy conversion to non-thallium-containing products. Since thallium and its compounds are extremely toxic and the poisoning is cumulative, they must be handled with rubber gloves and all operations must be conducted in a hood. Moreover, the thallium-containing residues must be collected and disposed of under special conditions.²

Organometallic Chemistry of Tl(I). The major uses of Tl(I) salts are for selective alkylations and acylations. Thallous alkoxides react with 1,3-dicarbonyl compounds in nonpolar solvents to give salts that are useful intermediates for alkylated or acylated derivatives (Scheme I):



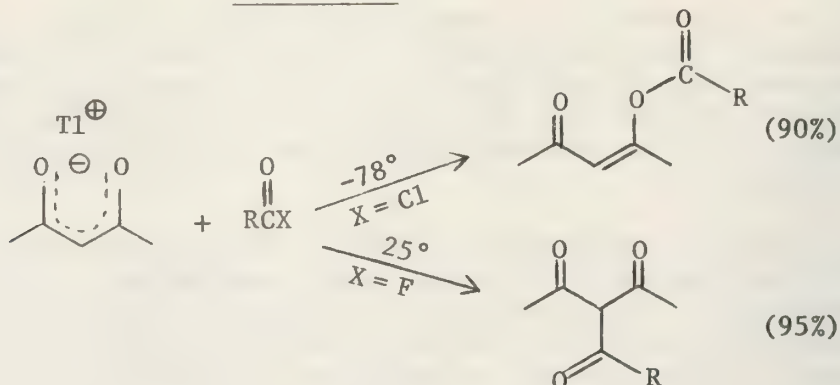
Heating of Tl(I) salts with alkyl iodides results in regiospecific C-alkylation in virtually quantitative yield³ (Scheme II):



Thallous ethoxide is most often used in these reactions as it is soluble in organic solvents. It is striking that none of the usual side reactions accompanying alkylation of alkali metal salts of ambident anions is observed (dialkylation, Claisen condensation, etc.). High yields of

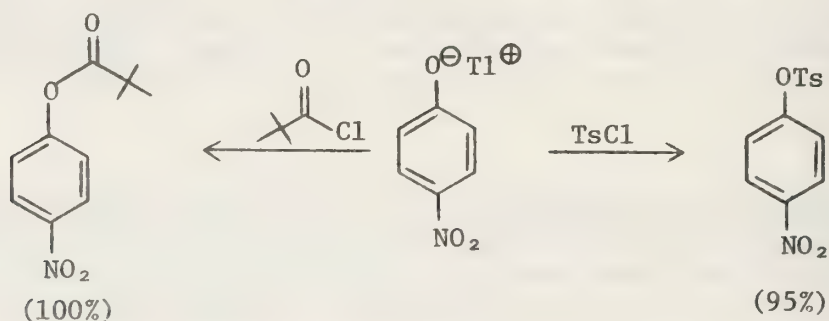
monoacylated products can also be obtained, and regiospecifically³ (C- versus O- acylation, Scheme III):

Scheme III



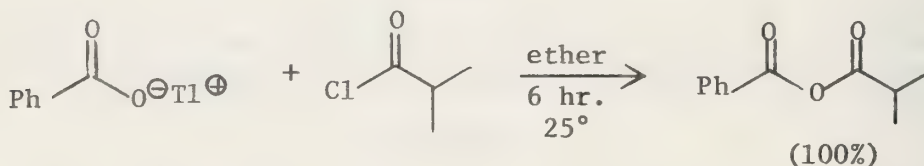
Thallous alkoxides have also been used for acylation and tosylation of phenols⁴ (Scheme IV):

Scheme IV



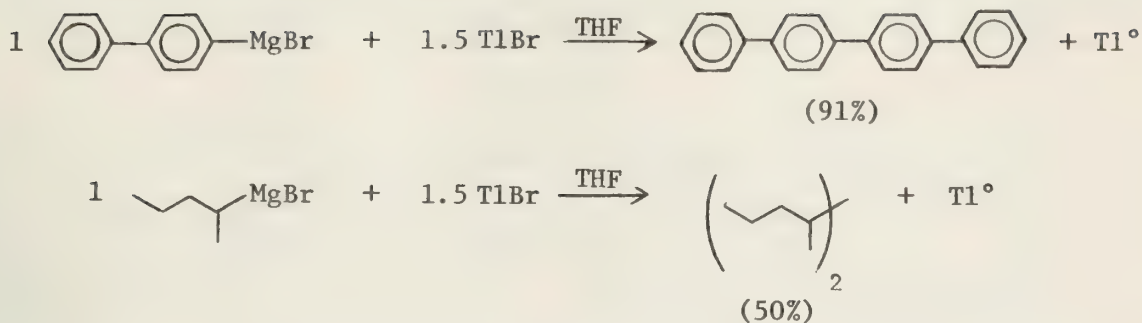
Thallium(I) carboxylates are useful for efficient and mild synthesis of symmetrical and unsymmetrical anhydrides. Treatment of Tl(I) carboxylates with one equivalent of acid halide followed by filtration of Tl(I) halide and evaporation of solvent gives the anhydride in quantitative yield⁴ (Scheme V):

Scheme V



Thallium bromide was found to be an extremely efficient reagent for synthesis of biaryls and hydrocarbons by coupling of aromatic and aliphatic Grignard reagents⁵ (Scheme VI):

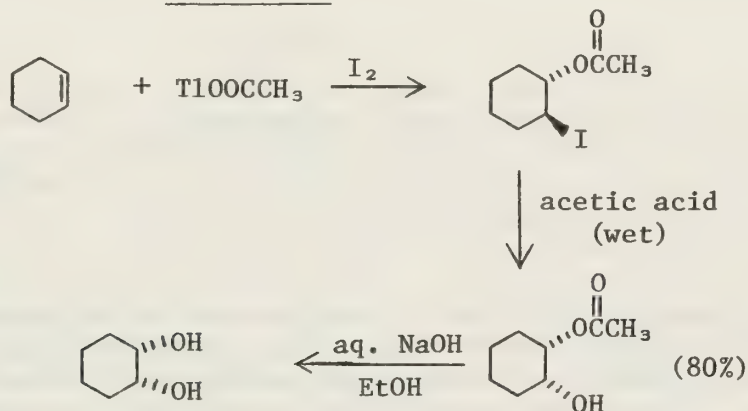
Scheme VI



The mechanism of this reaction appears to be fairly complex, and investigation indicated that all three of the valence states of thallium are involved.

Treatment of alkenes with Tl(I) carboxylate and iodine gives high yields of trans-1,2-iodo carboxylates which can be hydrolyzed to cis glycols⁶ (Scheme VII):

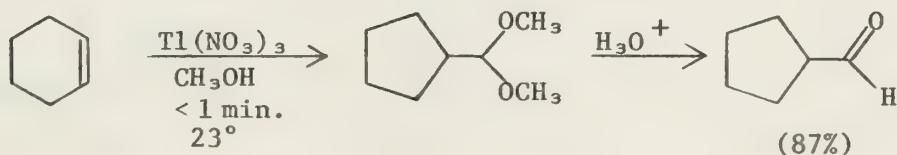
Scheme VII



Organometallic Chemistry of Tl(III). The high degree of electrophilicity and strong tendency for reduction of Tl(III) to Tl(I) make Tl(III) an effective oxidizing agent for electron-rich organic substrates.

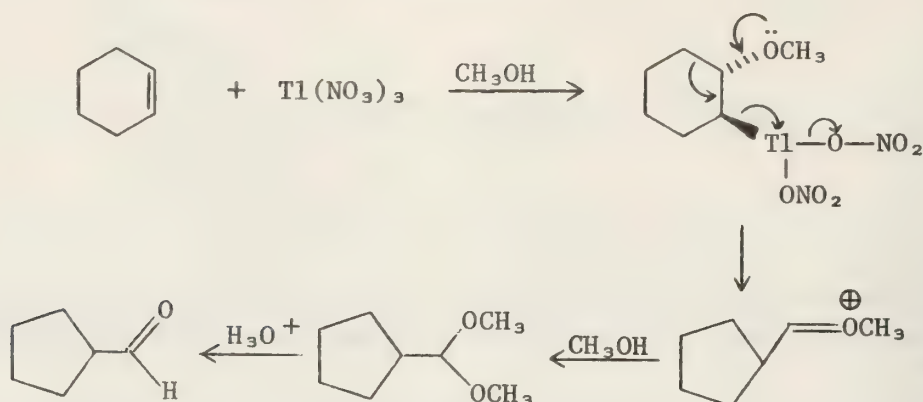
Oxythallation is the oxidative addition of TlX_2^+ and an oxyanion ($-\text{OH}$, $-\text{OR}$, $-\text{O}_2\text{CR}$) to the double bond of an olefin. This process is followed by cleavage of the Tl-C bond to give oxidized products and TlX (reductive elimination). An example of oxidative rearrangement by oxythallation is the following⁷ (Scheme VIII):

Scheme VIII



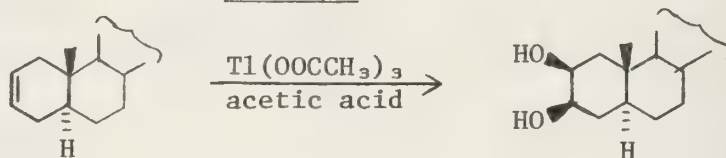
The proposed mechanism for this conversion is outlined below⁷ (Scheme IX):

Scheme IX



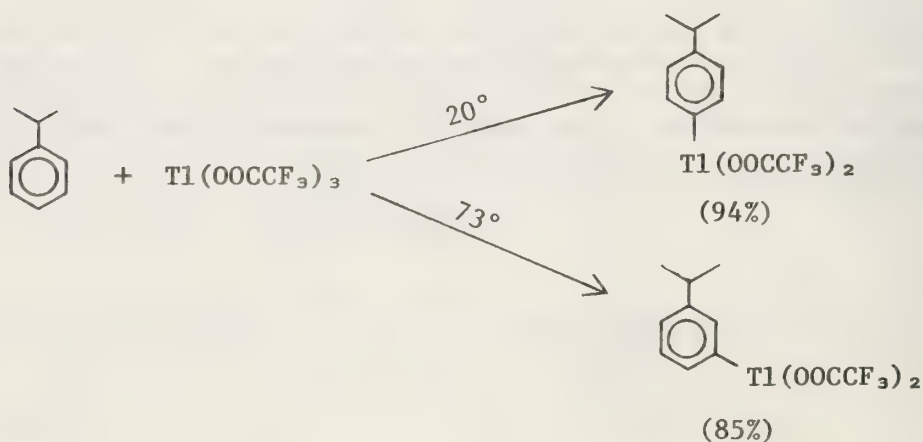
Cis hydroxylations of disubstituted steroidal olefins from the hindered side of the molecule have been accomplished using thallium(III)⁸ (Scheme X):

Scheme X



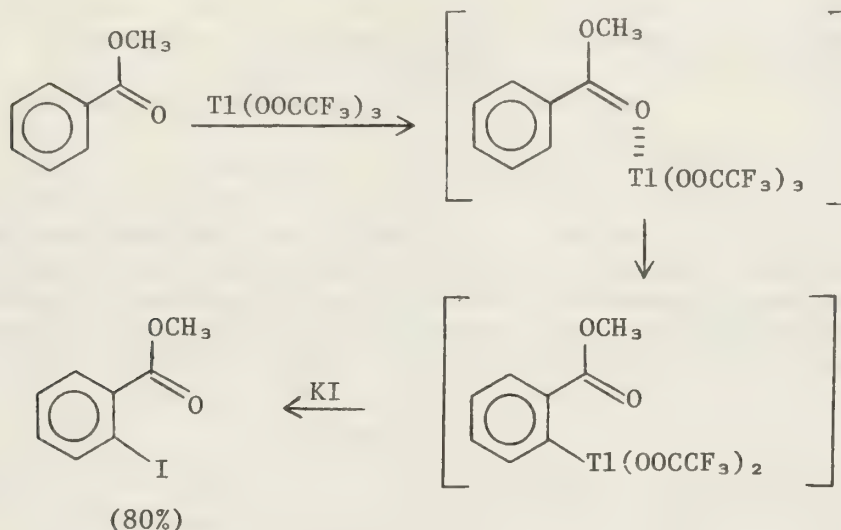
Aromatic thallation is an electrophilic substitution reaction with a moderately large energy of activation (27 kcal/mole) and an extremely large steric demand because of the size of TlX_2^+ . The result of the latter feature is a preference for para substitution. Under conditions of kinetic control (low temperature, short reaction time), the para substituted product is obtained. At high temperature and long reaction time (thermodynamic control) the meta isomer is the major product^{9,10} (Scheme XI):

Scheme XI



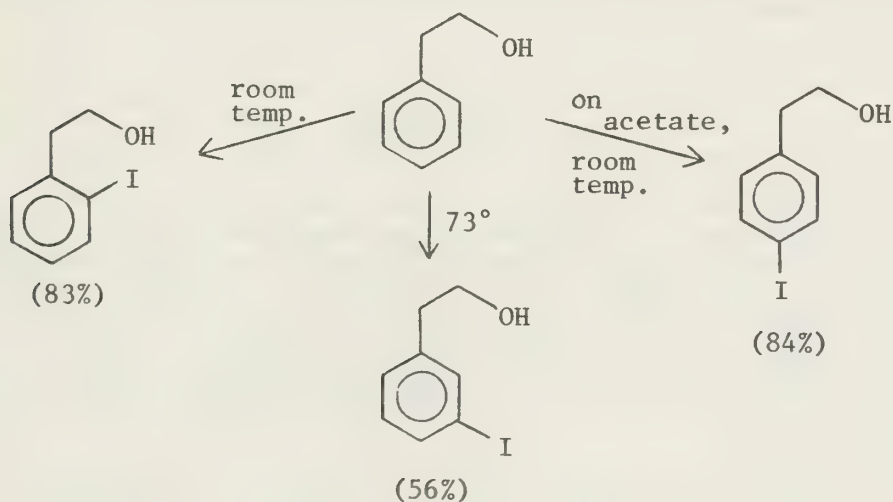
Interestingly, thallation of methyl benzoate occurs at the ortho position in a process due to the intermediacy of a substrate-electrophile complex that delivers thallium intramolecularly to the ortho position (Scheme XII):

Scheme XII



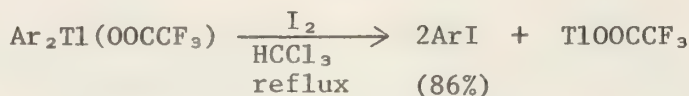
Predominant ortho substitution is also seen with benzyl alcohol and benzyl methyl ether. It is thus possible in some cases to give selective ortho, meta, or para substitution with the same substrate. The selective conversion of 2-phenylethanol to its ortho-, meta-, or para-iodo-substituted product illustrates this. Thallation at room temperature (kinetic control) gives predominantly ortho substitution (83%) (due to the complexing effect of the hydroxyl group), while thallation at 73° (thermodynamic control) gives predominantly meta substitution (56%). Thallation of the acetate of 2-phenylethanol, however (where the distance of the complexed $\text{Tl}(\text{OOCCF}_3)_3$ from the ring has been increased by conversion of OH to OCOCH_3), results in predominantly para substitution^{9,10} (84%) (Scheme XIII):

Scheme XIII



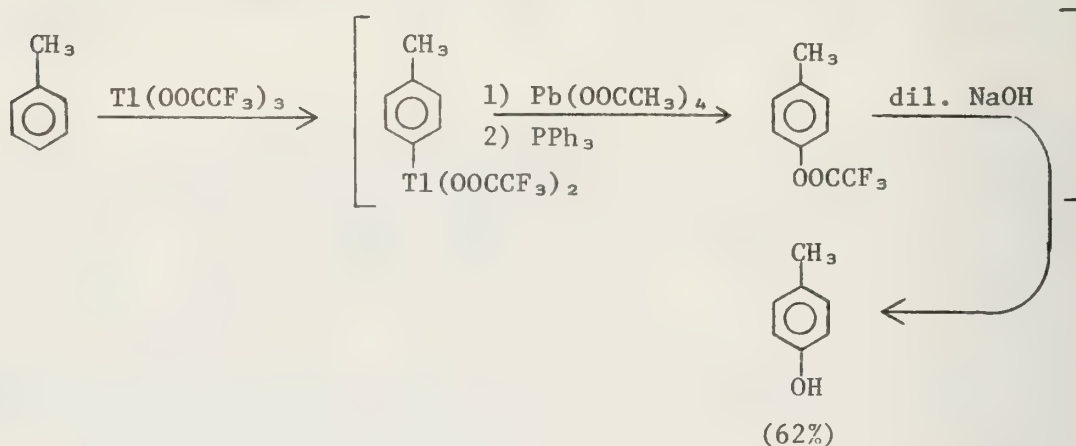
These arylthallium ditrifluoroacetates are versatile intermediates for the synthesis of a wide variety of selectively substituted aromatic compounds. The synthesis of aryl iodides from diarylthallium compounds has also been described by Taylor and McKillop¹¹ (Scheme XIV):

Scheme XIV



A "one-step" synthesis of phenols from arylthallium compounds has been reported. Addition of lead tetraacetate to a solution of the aryl thallium compound in trifluoroacetic acid, followed by addition of triphenylphosphine and workup in basic solution, gives the phenol¹² (Scheme XV):

Scheme XV



These selected examples have illustrated some of the uses of organo-thallium intermediates, and they serve to demonstrate the utility of thallium in organic synthesis.

BIBLIOGRAPHY

1. A. McKillop and E. C. Taylor, *Chem. Brit.*, **9**, 4 (1973).
2. E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3**, 338 (1970).
3. (a) E. C. Taylor, G. H. Hawks III, and A. McKillop, *J. Am. Chem. Soc.*, **90**, 2421 (1968). For examples of use, see K. B. Sloan and N. Bodor, *J. Org. Chem.*, **41**, 165 (1976); G. Büchi, K.-C. Luk, and P. M. Müller, *J. Org. Chem.*, **40**, 3458 (1975); (b) Some workers feel this technique offers no advantages for exclusive mono-C-alkylation: J. Hooz and J. Smith, *J. Org. Chem.*, **37**, 4200 (1972).
4. E. C. Taylor, G. W. McLay, and A. McKillop, *J. Am. Chem. Soc.*, **90**, 2422 (1968). For an example of use, see J. L. Bloomer and F. E. Kappler, *J. C. S. Perkin I*, 1485 (1976).

5. A. McKillop, L. F. Elson, and E. C. Taylor, *J. Am. Chem. Soc.*, 90, 2423 (1968). For an example of use, see P. M. Henry, *J. Org. Chem.*, 35, 3083 (1970).
6. R. C. Cambie, R. C. Hayward, J. L. Roberts, and P. S. Rutledge, *J. C. S. Perkin I*, 1120, 1858 (1974).
7. A. McKillop, J. D. Hunt, F. Kienzle, E. Brigham, and E. C. Taylor, *J. Am. Chem. Soc.*, 95, 3635 (1973). For examples of use, see M. Anteunis and A. DeSmet, *Synthesis*, 12, 868 (1974); F. J. McQuillin and D. G. Parker, *J. C. S. Perkin I*, 2092 (1975); A. Lethbridge, R. O. C. Norman, C. B. Thomas, and W. J. E. Parr, *J. C. S. Perkin I*, 231 (1975).
8. E. Glotter and A. Schwartz, *J. C. S. Perkin I*, 1660 (1976).
9. E. C. Taylor, F. Kriengle, R. L. Robey, and A. McKillop, *J. Am. Chem. Soc.*, 92, 2175 (1970).
10. E. C. Taylor, F. Kriengle, R. L. Robey, A. McKillop, and J. D. Hunt, *J. Am. Chem. Soc.*, 93, 4845 (1971). For examples of use, see S. F. Dyke and E. P. Tiley, *Tetrahedron*, 31, 561 (1975); W. Carruthers and R. Pooranamoorthy, *J. C. S. Perkin I*, 2405 (1974).
11. E. C. Taylor, H. Atland, and A. McKillop, *J. Org. Chem.*, 40, 2351 (1975).
12. E. C. Taylor, H. W. Atland, R. H. Danforth, G. McGillivray, and A. McKillop, *J. Am. Chem. Soc.*, 92, 3520 (1970). For an example of use, see B. Davies and C. B. Thomas, *J. C. S. Perkin I*, 65 (1975).

MONOMERIC METAPHOSPHATE

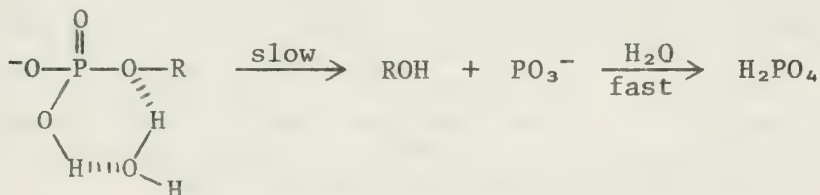
Reported by Charles W. Perkins

May 8, 1978

In the 1940's, Bailey^{1,2} and Desjoberg^{3,4} found a distinctive relationship between the rate of hydrolysis of ethyl phosphate and pH. A maximum rate was observed around pH = 4 that steadily decreased as the pH was increased. The rate also decreased as the pH was lowered from 4 until a minimum was reached between 0 and 1. Then, as more acid was added, the rate began to rise again. Around pH = 4 is the acidity region where the monoanion is at its greatest concentration. This suggests that the rate of hydrolysis is linear with the concentration of the monoanion and that the monoanion may have available to it a lower energy pathway for hydrolysis that is not available to the neutral species or the dianion. This behavior is common to many of the monoesters of phosphoric acid but not to the di- or triesters.⁵

Cleavage of P-O was demonstrated in the hydrolysis of methoxyethyl phosphate⁶ at pH = 4 and 8.5 both by stereochemical and isotope tracer studies. This finding, coupled with the pH profile, prompted Westheimer to propose a mechanism involving monomeric metaphosphate.⁷

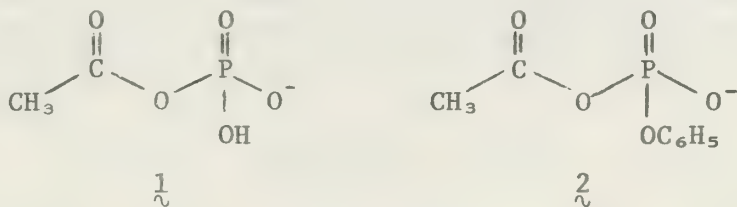
The Westheimer proposal, which involves a proton transfer during or prior to the rate-determining step of the reaction, explains the P-O cleavage, the increased rate of the monoanion over the dianion, and the increased rate of monoanion over the neutral species.



A careful study of the dissociation constants of methyl phosphoric acid⁸ permitted calculation of the concentration of the monoanion at various pH values. An almost perfect fit of the hydrolysis rates vs. pH is obtained by using the rate law: $\text{rate} = k_1[\text{MeOPO}_3\text{H}^-]$.⁹

Subsequently, a large body of evidence has been amassed in support of the above mechanism for hydrolysis of various monoesters of phosphoric acid which may be summarized in the following way:

a) The small ΔS^\ddagger for the hydrolysis of many monosubstituted esters¹⁰⁻¹² is in sharp contrast to the values of variously substituted analogues: ΔS^\ddagger of **1** is -3.6 eu while that of **2** is -28.8 eu.



b) ΔV^\ddagger for the hydrolysis of **1** is $0.6 \pm 1 \text{ cm}^3/\text{mol}$, while the ΔV^\ddagger for **2** is $-19 \pm 2 \text{ cm}^3/\text{mol}$.¹¹ Large negative ΔV^\ddagger values are expected for bimolecular reactions.

c) Variation of ionic strength had little effect on hydrolysis of $\frac{1}{\nu}$ whereas concentrated salt solutions considerably decreased the rate of hydrolysis of 2.8 .⁸ A similar disparity was observed upon addition of 30-50% acetonitrile.⁸

d) A plot of $\log(\text{rate})$ vs. pK_a gives a straight line with a slope of -0.27 , which indicates very little sensitivity to the structural differences of leaving groups.¹³ This finding supports the notion of a concerted or preequilibrium proton transfer.

e) There are varying solvent isotope effects depending on the nature of the leaving group. Those with $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} < 1$ are thought to involve proton transfer prior to the rate determining step. Those with $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} > 1$ have the proton transfer involved in the rate determining step.

Two paradigm cases are monomethyl phosphate and 2,4-dinitrophenyl phosphate (2,4-DNPP). For the monomethyl case, the $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ is 0.87, consistent with proton transfer prior to the rate determining step. The rate is proportional to the protonated intermediate.

The 2,4-dinitrophenyl case entails a concerted cleavage and proton transfer: $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.45$.¹⁵ In this case, the leaving group is stable enough to cause the rate of cleavage to be competitive with proton transfer.

There are molecules in which the leaving group is stable enough to depart entirely without proton transfer.¹¹ In these cases, the dianion is also thought to decompose by the metaphosphate route. Electron withdrawing groups would be expected to increase the rate. A Hammett σ - ρ relationship observed in benzoyl esters confirms this prediction. Predictably, also, hydrolysis of monoanions should not change in D_2O , which is true to observation.¹¹ If the hydrolysis rates of the dialkyl esters are much slower than those of the monoalkyl analogues, this observation is a consequence of different mechanistic routes.^{16,17}

The foregoing represents, up to the last decade, the main body of evidence in support of the monomeric metaphosphate mechanism for hydrolysis of the monoesters of phosphoric acid.^{5,14} For examples of other types of reactions that are thought to involve the metaphosphate as an intermediate, see Emsley.¹⁴

More recent investigations add to the preponderance of evidence for the existence of monomeric metaphosphate. ^{18}O isotope effects were observed^{18,19} in the rate of hydrolysis of ^{16}O - and ^{18}O -2,4-dinitrophenyl phosphate. An average of 32 runs gave an isotope ratio of 1.0204 ± 0.0044 . From this value it can be stated with 99% confidence that at least some isotope effect is experimentally verifiable. The ^{18}O isotope effects can be used to study the extent of bond cleavage in the transition state.²⁰⁻²² A mathematical approximation of the extent of cleavage may be obtained from:

$$k_{16}/k_{18} = e^{[hc(\Delta\nu^r - \Delta\nu^\ddagger)/2kT]}$$

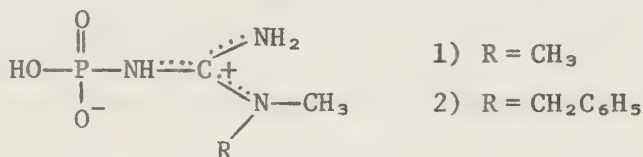
The P-O stretching frequency in the reactant (1200 cm^{-1}) is reduced to 650 cm^{-1} in the transition state. This is fully consistent with the expected P-O bond cleavage required by the metaphosphate mechanism. A 2% ^{18}O isotope effect is thought to represent nearly complete P-O cleavage. The

delocalization of the developing negative charge in the aryl oxygen, increasing the C-O bond order, will partially attenuate the effect of the loss of P-O stretch. This results in a smaller isotope effect than would otherwise be expected.

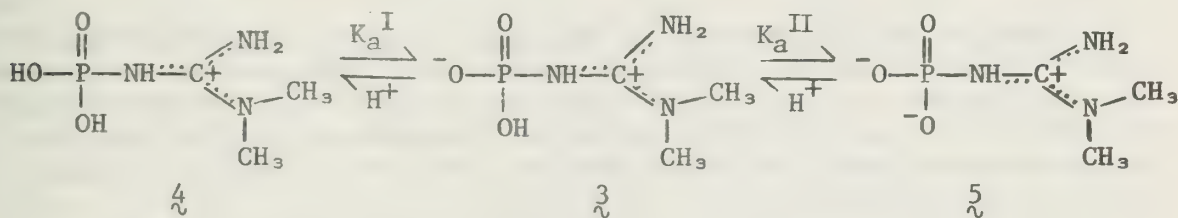
Pyridine, 2,6-lutidine and 1,4-dioxane have all been observed to catalyze the hydrolysis of 2,4-DNPP.²³ Pyridine has the most dramatic effect. As a consequence of its large negative ΔS^\ddagger (-23.9 eu) and favorable ΔH^\ddagger (15.8 kcal/mol) in comparison to the spontaneous hydrolysis ($\Delta S^\ddagger = 5.3$ eu, $\Delta H^\ddagger = 25.8$ kcal/mol), the pyridine catalyzed hydrolysis appears to go through an $S_N2(P)$ type of reaction.

2,6-Lutidine and 1,4-dioxane had much less catalytic effect than pyridine. Although the molecularity of the hydrolysis with dioxane present was second order, the ΔS^\ddagger was very low. This may indicate that the dioxane preferentially solvates the metaphosphate but does not bond to it during the transition state. It appears that these are varying degrees of bonding by the assisting nucleophile in these various hydrolyses. 2,6-Lutidine (being too sterically hindered to attack the phosphorus) and 1,4-dioxane lend solvational stability to the metaphosphate while pyridine gives nucleophilic assistance to the departure of the leaving group. It is noteworthy that the monoester hydrolysis, in almost all parameters studied, is very different from those reactions which almost certainly go through either a pentavalent transition state or a pentavalent intermediate.

In an attempt to understand the phosphorylitic reactions of phosphagens,²⁴ Haake and Allen²⁵ studied the hydrolysis of two phosphoroguanidines, N,N-dimethyl-N'-phosphoroguanidine (DMPG) and N-benzyl-N-methyl-N'-phosphoroguanidine (BMPG).



The rate profiles were measured spectrophotometrically by following the decrease in absorbency of the starting phosphoroguanidine. The pH vs. observed first order rate constants gave a bell-shaped curve very similar to the ones found for the monoalkyl esters. The experimental points for both BMPG and DMPG could be fit beautifully by using the rate equation, $\text{rate} = k_0[\text{AH}]$. [AH] is species 3 which is in equilibrium with species 4 and 5.



A few mathematical deductions were used to check this kinetic scheme:

$$\text{rate} = k_{\text{obvd}}[A]_{\text{total}} = k_o[AH]$$

$$\therefore k_{\text{obvd}} = \frac{k_o}{1 + [H+]/K_a^I + K_a^{II}/[H+]}$$

$$\text{when pH} > 2.5, K_a^I \gg [H+]$$

$$\therefore k_{\text{obvd}} = k_o - \frac{k_{\text{obvd}}}{[H+] K_a^{II}}$$

A plot of k_{obvd} vs. $\frac{k_{\text{obvd}}}{[H+]}$ should yield k_o as the y intercept and K_a^{II} as the negative slope. The graph did yield a straight line for both BMPG and DMPG.

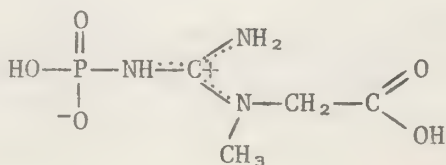
When $\text{pH} < 1.5$, $K_a^{II} \ll [H+]$ and $k_{\text{obvd}} = k_o - \frac{k_{\text{obvd}} [H+]}{K_a^I}$, plotting k_{obvd} vs. $k_{\text{obvd}} [H+]$ gave a straight line for both K_a^I BMPG and DMPG, with k_o the y intercept and $1/K_a^I$ the negative slope.

The k_o values obtained by both graphs were in good agreement. The K_a^{II} s were checked by potentiometric titrations. The data are entirely consistent with the neutral DMPG and BMPG being the reactive species in their respective reactions.

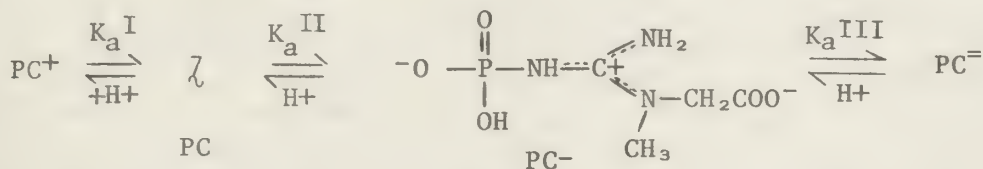
The ΔS^\ddagger values for the hydrolysis of DMPG and BMPG were 0.4 eu and -1.2 eu, respectively. The solvent deuterium isotope ratios were 0.90 and 0.86 for DMPG and BMPG. The monoanion 5 was found to be stable to hydrolysis at $\text{pH} = 9.5$, undergoing hydrolysis 10^4 times more slowly than 3. The monobenzyl ester of DMPG (6) was also found to be stable. At $\text{pH} = 1.85$, the absorbance of 6 was unchanged during seven days. As noted above, these data are all supportive of and consistent with the monomeric metaphosphate mechanism with a proton transfer.

The $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ value of less than 1.00 for DMPG indicates that the proton is transferred prior to the rate determining step. Phosphoramidate, $-\text{HO}_3\text{PNH}_3^+$, in which a proton transfer is not possible, has $\Delta S^\ddagger = -18.2$ eu, and its monomethyl ester is hydrolyzed at about the same rate as the parent acid.²⁶ These observations are in striking contrast to the behavior of the monobenzyl ester and the ΔS^\ddagger of DMPG as cited above. In DMPG and BMPG, the availability of an unshared pair of electrons on N is an essential element in the increased reactivity of the neutral species.

Since phosphocreatine (7) is the main phosphorylating phosphoguanidine and in biological systems exists at $\text{pH} = 7$, it is thought that the enzyme acts as a proton transfer agent. The hypothesis is that creatine kinase situates an ADP molecule adjacent to the phosphate moiety so that the metaphosphate may be quickly converted to ATP, subsequent to P-N bond cleavage and proton transfer.



An analysis similar to the one used in the phosphoquanidine hydrolysis study was used in the hydrolysis study of 7.²⁷ In the more recent study, an extra ionizable proton and a mixture of products complicate the study. The extra proton creates two reactive species rather than one.

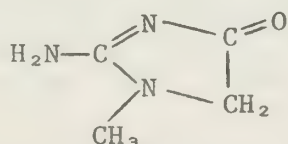


First order kinetics were observed both by following the production of inorganic phosphate and creatine and creatinine. By multiplying k_{obvd} by mole fraction, χ_A , for creatine and χ_B for creatinine, one may obtain k_A and k_B values for the first-order rate constants for each product and thus allow separate kinetic treatment for the formation of each product.

The rate expression for the hydrolysis is: $\text{rate} = k_A[\text{PC}]_T = k_1[\text{PC}] + k_2[\text{PC}^-]$, which may be reduced to: $k_A = k_2 - k_A \frac{K_a^{\text{III}}}{[\text{H}^+]}$ at $\text{pH} > 3.5$.

A plot of k_A against $\frac{k_A}{[H^+]}$ is linear and gives K_a^{III} as a negative slope, k_2 as the y intercept. K_a^{III} , determined potentiometrically, agrees closely with K_a^{III} obtained from the hydrolysis data. At values of pH 1, a plot of k_A vs. $k_A[A^+]$ gives K_a^I and k_1 . Using k_1 and K_a^{III} found in this manner and K_a^{II} and K_a^I determined potentiometrically, one may obtain a curve that fits the data for the production of creatine from the hydrolysis.

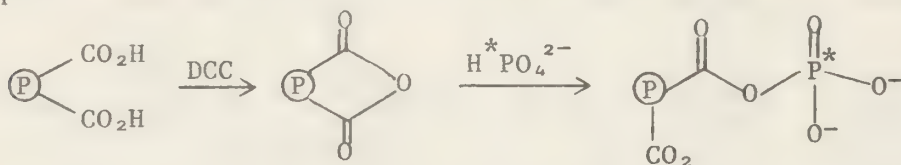
Creatinine was the major product only at very low pH. The rate for creatinine production was expressed as: $\text{rate} = k_B[\text{PC}]_{\text{TOTAL}} = k_3[\text{H}^+][\text{PC}^+] + k_4[\text{PC}^+] + k_5[\text{PC}] + k_6[\text{PC}^-]$ (equation 1). The same type of mathematical gymnastics as used above led to the assignment of k_3 , k_4 ,



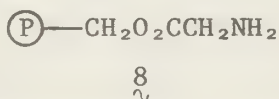
Creatinine

k_5 , k_6 , and K_a^{III} . K_a^{III} found in this manner agreed with the potentiometric titration. When k_3 , k_4 , k_5 , k_6 , K_a^I , K_a^{II} , K_a^{III} were all used, equation 1 gave a curve that fit the experimental data; thus, the rate equations were well justified by the data. The ΔS^\ddagger for the reaction was determined to be -2 ± 5 eu, close enough to 0 to be indicative of a unimolecular reaction. The deuterium isotope effect was found to be $k_{H_2O}/k_{D_2O} = 0.89$. The monomeric metaphosphate mechanism with a proton transfer involved in the rate-determining step is suggested for both neutral phosphocreatine and the deprotonated analogue. One might have expected the carboxylic proton to catalyze the reaction for PC, but no catalytic effect was indicated. The values for k_1 and k_2 are similar, and the neutral phosphocreatine is hydrolyzed more slowly than DMPG. The slower rates for both PC and PC- are likely due to the electronic effect of the carboxy group that lowers the basicity of the N of the P-N bond.

Rabeck and Gavina have developed a new technique²⁸ for detecting intermediates which they have applied²⁹ to the detection of the monomeric metaphosphate. Phosphorus-labeled, polymer-bound acyl phosphate was first prepared.



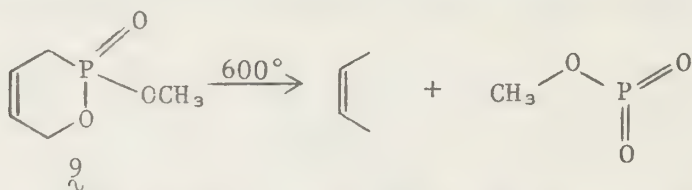
The scheme involves suspending the polymer-bound acyl phosphate together with polymer-bound glycine at 80°C and observing the ³²P phosphate transfer to 8.



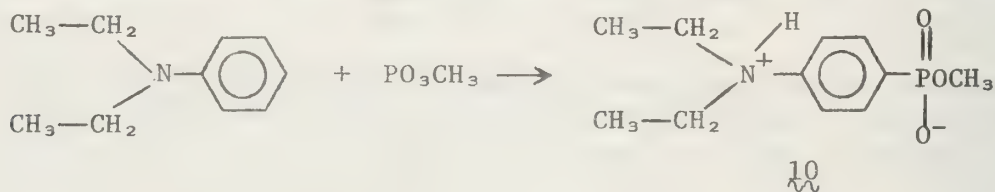
The product from phosphorylation of 8 was saponified to yield glycine-N-phosphate containing the radiolabel.

Since the resin bead surfaces are not thought to react to any significant degree,³⁰ the presence of a phosphorylation reagent in solution was thus established. The phosphorylating agent could be the monomeric metaphosphate, but the possibility of its higher oligomers being that agent has not been disproved. The dimer, pyrophosphate, has been eliminated because of its inability to phosphorylate 8 under the same conditions. There was no mention of an attempt to phosphorylate with higher oligomers.

Westheimer³¹ was able to trap methyl metaphosphate. From the pyrolysis of methyl-2-butenylphosphonate, 9, methyl metaphosphate was



generated in the gas phase. The methyl metaphosphate was observed to attack N,N-diethylaniline to produce the methyl ester of p-diethylaminobenzenephosphoric acid 10. The structure of 10 was verified by



comparing its ¹H nmr with that of a separately synthesized sample. In an earlier study, methyl metaphosphate in gas phase was observed to attack N-methyl aniline to yield the product of attack on N.³²

On the basis of extended Huckel and CINDO/2 MO calculations,³³ it was found that monomeric metaphosphate has energetically close, low-lying π^* and σ^* acceptor orbitals centered mainly on phosphorus. The π^* and σ^*

orbitals extend spatially much further than they do on NO_3^- . The electrophilicity of this anionic Lewis acid can be explained by these phosphorus localized, spatially extended, low-lying π^* and σ^* orbitals which are suitably located for significant interaction with donor orbitals. Donor orbitals may begin to interact without any significant electron repulsion. The consequence is a lower ΔH^\ddagger . A more favorable ΔS^\ddagger is conferred upon the PO_3^- over that of NO_3^- by the more greatly extended acceptor orbitals as well as by a greater amount of insipient electron density along a path perpendicular to the molecular plane. The latter approach does not optimize orbital overlap and may have a minimal effect.

FOOTNOTES AND REFERENCES

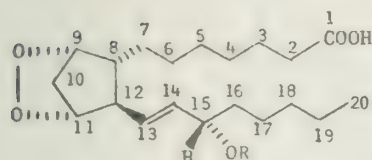
1. M. C. Bailey, *Bull. Soc. Chem. France*, 9, 421 (1942).
2. M. C. Bailey, *Bull. Soc. Chem. France*, 9, 340, 405 (1942).
3. A. Desjobert, *Compt. Rend.*, 224, 575 (1947).
4. A. Desjobert, *Bull. Soc. Chem. France*, 14, 809 (1947).
5. J. R. Cox and O. B. Ramsey, *Chem. Rev.*, 64, 317 (1964).
6. W. W. Butcher and F. H. Westheimer, *J. Am. Chem. Soc.*, 77, 2420 (1955).
7. The monomeric metaphosphate was apparently first proposed by A. R. Todd in the Arthur D. Little Lectures at M.I.T. in 1954.
8. C. H. Bunton, D. R. Llewellyn, *et al.*, *J. Chem. Soc.*, 3574 (1958).
9. This fit is over pH ranging from 1 to very alkaline. At pH <1 other mechanism(s) begin to affect the rate; as evidenced by significant C-O cleavage.
10. J. D. Chanley and E. Fergeson, *J. Am. Chem. Soc.*, 77, 4002 (1955).
11. G. DiSabato and W. P. Jencks, *J. Am. Chem. Soc.*, 83, 4400 (1961).
12. C. H. Bunton, *et al.*, *J. Chem. Soc.*, 3588 (1958).
13. Exceptions occur when the leaving group is stable enough to depart without protonation.
14. J. Enesley and D. Hall, "The Chemistry of Phosphorus", Halsted Press, New York, New York, 1976, Ch. 8.
15. A. J. Kirby and A. G. Varvoglis, *J. Am. Chem. Soc.*, 89, 415 (1967).
16. R. J. Bentley, *J. Am. Chem. Soc.*, 71, 2765 (1949).
17. J. H. Park and D. E. Koshland, Jr., *J. Biol. Chem.*, 233, 986 (1958).
18. D. G. Gorenstein, *J. Am. Chem. Soc.*, 94, 2523 (1972).
19. D. G. Gorenstein, Y. G. Lee, and K. Debojyati, *J. Am. Chem. Soc.*, 99, 2264 (1977).
20. C. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1964, pp. 315-317.
21. A. Fry, "Isotope Effects in Chemical Reactions," Van Nostrand, New York, N. Y., 1970, Ch. 6.
22. J. Bigelusen, *J. Chem. Phys.*, 17, 675 (1949).
23. A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc.*, 135 (1968).
24. Phosphagenes are acid labile phosphorus-containing compounds contained in most vertebrate muscle tissue.
25. P. Haake and G. W. Allen, *J. Am. Chem. Soc.*, 95, 8080 (1973).
26. I. Ohney and M. Coplow, *J. Am. Chem. Soc.*, 89, 6972 (1967).
27. P. Haake and G. W. Allen, *J. Am. Chem. Soc.*, 48, 4990 (1976).
28. J. Rabek and F. Gavina, *J. Am. Chem. Soc.*, 97, 1591 (1975).
29. J. Rabek and F. Gavina, *J. Am. Chem. Soc.*, 97, 3221 (1975).
30. J. Rabek, D. Brown, and S. Zimmerman, *J. Am. Chem. Soc.*, 97, 4541 (1975).
31. F. H. Westheimer, C. H. Clapp, A. Satterthwait, *J. Am. Chem. Soc.*, 97, 6873 (1975).
32. F. H. Westheimer, C. H. Clapp, *J. Am. Chem. Soc.*, 96, 6710 (1974).
33. L. M. Loew and W. R. MacArthur, *J. Am. Chem. Soc.*, 99, 1019 (1977).

PROSTAGLANDIN ENDOPEROXIDES: MODELS FOR THEIR BIOSYNTHESIS AND CHEMISTRY

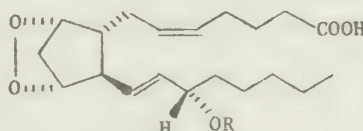
Reported by Steven Hobbs

May 11, 1978

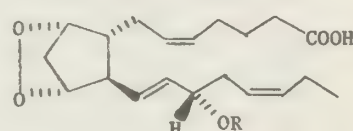
Introduction. The prostaglandin endoperoxides PGG_1 (1), PGG_2 (2), PGG_3 (3), PGH_1 (4), PGH_2 (5), and PGH_3 (6) are pivotal intermediates in the biosynthesis of prostaglandins, as well as the thromboxanes, prostacyclins and other metabolites. Intense research efforts have been inspired by these novel peroxides primarily along four lines: 1) elucidation of the mechanism of biosynthesis of prostaglandin endoperoxides from their fatty acid precursors, 2) chemical synthesis and characterization of prostaglandin endoperoxides, 3) elucidation of the mechanism of prostaglandin endoperoxide rearrangements to prostacyclin, thromboxanes and other metabolites, and 4) imitation of the biological activity of prostaglandin endoperoxides via compounds lacking the peroxide linkage. In this seminar, we will discuss the chemical models used to explore the first and third lines of research interests.



1 $\text{R} = \text{OH}$, PGG_1
4 $\text{R} = \text{H}$, PGH_1



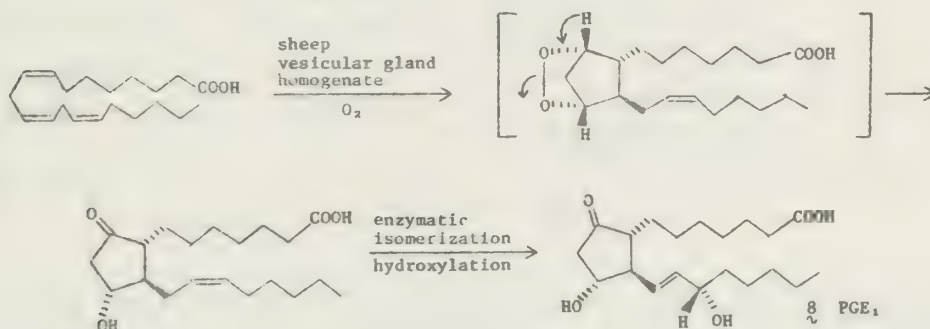
2 $\text{R} = \text{OH}$, PGG_2
5 $\text{R} = \text{H}$, PGH_2



3 $\text{R} = \text{OH}$, PGG_3
6 $\text{R} = \text{H}$, PGH_3

Prostaglandin Endoperoxides - Isolation, Biological Transformations, Biosynthesis and Biological Activity.¹ Prostaglandin endoperoxides were first proposed as intermediates in prostaglandin biosynthesis by Samuelsson to explain the derivation of the 9,11 oxygens of PGE_1 (8) from the same molecule of oxygen in its biosynthesis from all cis 8,11,14-eicosatrienoic acid (7) by vesicular gland homogenate, as determined by ^{18}O labeling studies (Scheme I).²

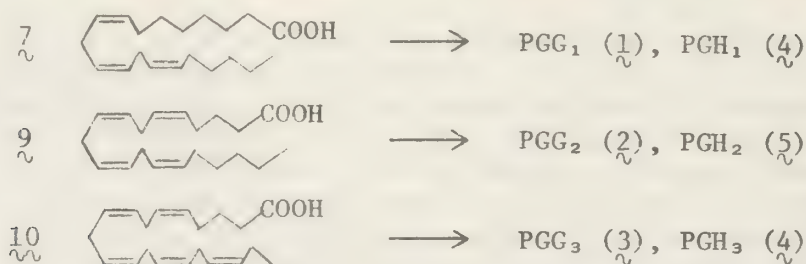
Scheme I



Isolation of Prostaglandin Endoperoxides. Prostaglandin endoperoxides of the G,H series have been isolated by the short term incubations of all cis 8,11,14-eicosatrienoic acid (7), 5,8,11,14-eicosatetraenoic acid (arachidonic acid) (9), and 5,8,11,14,17-eicosapentaenoic acid (10) with

the microsomal fractions of sheep seminal vesicle (a well-known prostaglandin synthesizing system), as in Scheme II.

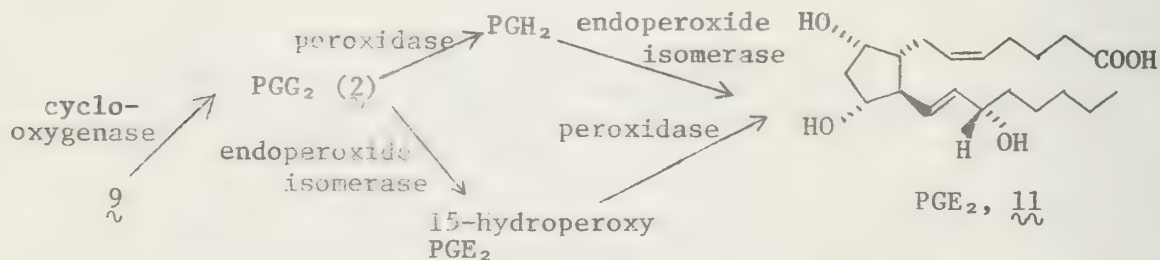
Scheme II



The first isolation of a prostaglandin endoperoxide was that of PGH₂ (5) methyl ester by Hamberg and Samuelsson, from the incubation of arachidonic acid (9) with sheep seminal vesicle homogenate. The structure proposed by the authors rested on chemical transformation of the methyl ester of 5 to known prostaglandins.³ Later work by Nugteren and Hazelhof provided indirect evidence for PGG₁ (1) and PGH₁ (4), formed from 7 in microgram quantities. Purified preparations of PGH₁ were stable in 9:1 (v/v) diethyl ether-methanol for several weeks at -80°C, but decomposed in 1:1 (v/v) light petroleum ether-diethyl ether with a half life of 2.7 hr at 20°C and in aqueous media (ph 4-8) with a half life of only 30 min at 20°C.⁴ PGG₂ (2) and PGH₂ (5) were isolated by Hamberg and Samuelsson under similar conditions used to isolate PGH₂ methyl ester. Both 2 and 5 were stable in dry ethyl ether or acetone at -20°C but decomposed readily upon addition of protic solvents such as water or ethanol.⁵ Further work by Needleman *et al.* has led to the isolation of PGG₃ (3) and PGH₃ (6) from the corresponding unsaturated acid 10.⁶ Recently, two groups have reported the isolation of prostaglandin endoperoxides in multimilligram amounts and have characterized them by ¹H NMR, IR and mass spectral data.⁷

Biosynthesis of Prostaglandin Endoperoxides. Studies of the transformations of arachidonic acid (9) by sheep vesicular gland homogenates suggest the possible origin of prostaglandin endoperoxides PGG₂ (2) and PGH₂ (5) by the pathway in Scheme III.^{1a,b}

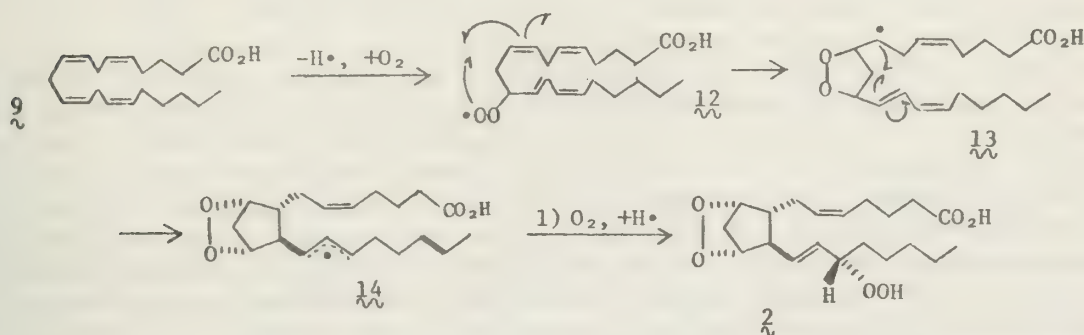
Scheme III



Recently, Miyamoto and co-workers have isolated and purified a "prostaglandin endoperoxide synthetase" from bovine vesicular gland consisting of two fractions, one capable of bringing about the transformation of all cis 8,11,14-eicosatrienoic acid (7) to PGG₁ (1) or PGH₁ (4), and have suggested the biosynthetic sequence 7 → 1 → 4 → 8 for prostaglandin endoperoxide biosynthesis.¹⁰

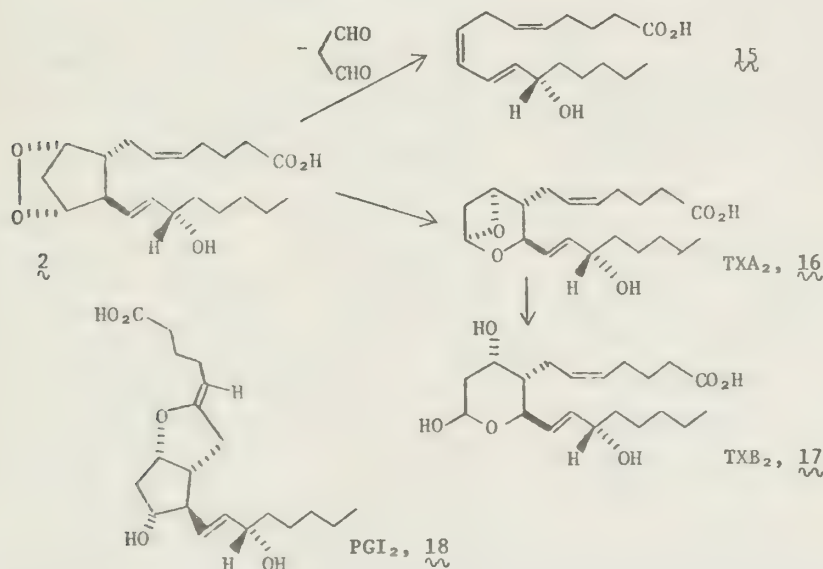
The mechanism of the cyclooxygenase¹¹ mediated conversion of arachidonic acid (9) to PGG₂ (2) has been proposed to be that of Scheme IV. A similar mechanism has been postulated for the formation of PGG₁ (1) from the corresponding acid 7.^{8,20}

Scheme IV



Biological Transformations of Prostaglandin Endoperoxides. Prostaglandin endoperoxides give rise to a wide variety of metabolites, some of these having unique biological activities. In sheep vesicular glands, PGG₂ (2) serves as a precursor to the prostaglandin PGE₂ (11) as in Scheme III. However, in human blood platelets, PGG₂ (2) is transformed into the highly labile thromboxane A₂ (16) and thromboxane B₂ (17) and also undergoes an apparent loss of malonaldehyde to form 12-L-hydroxy-5,8,10-heptadecatrienoic acid (15) as in Scheme V.^{1a,12} In addition, PGH₂ (5) serves as the precursor to prostacyclin PGI₂ (18).¹¹ The mechanistic details for these biological rearrangements of the prostaglandin endoperoxides are not known at this time.

Scheme V

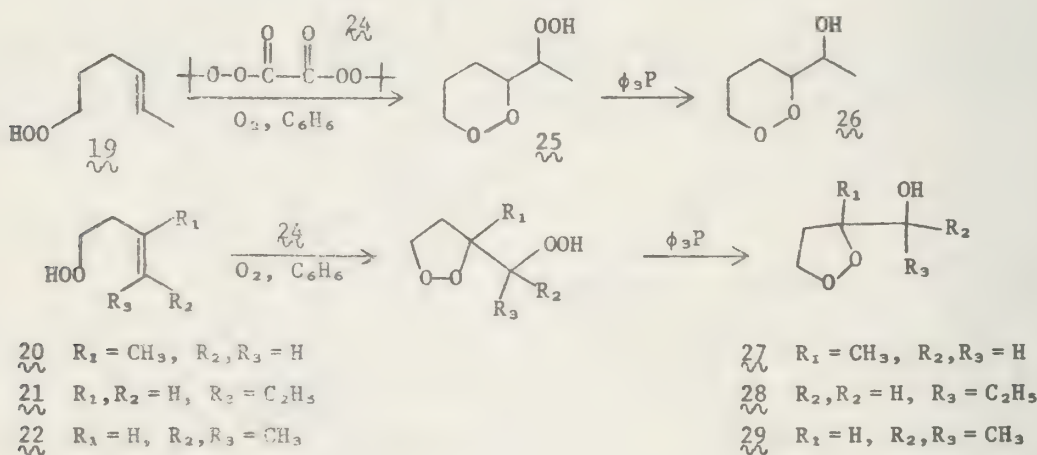


Biological Activities of Prostaglandin Endoperoxides. The biological effects of prostaglandin endoperoxides on a variety of tissues have been the subject of intense research interest for biochemists and several review articles on this subject have appeared.¹ Briefly, prostaglandin endoperoxides have two characteristic biological activities useful in their characterization: 1) they bring about contraction of a wide variety of

smooth muscle tissues, such as rabbit aorta, and 2) cause rapid, irreversible aggregation of human platelets (for PGH_2 (5) and PGG_2 (2)).^{1a} The role of prostaglandin endoperoxides in the platelet aggregation mechanism in concert with prostacyclin PGI_2 (18) and thromboxane A_2 (16) has been discussed elsewhere.¹¹

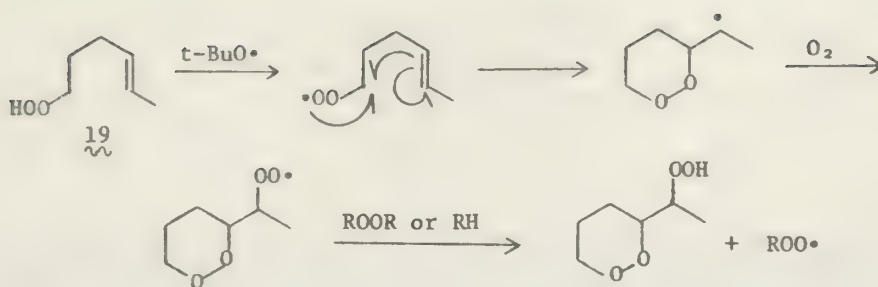
Models for the Peroxy Radical Cyclization Leading to Prostaglandin Endoperoxides. The mechanism of Scheme IV represents a hypothetical pathway for the cyclooxygenase mediated conversion of unsaturated fatty acids to their corresponding prostaglandin endoperoxides. Research efforts to verify this pathway have followed two lines: 1) studies of the nonenzymatic conversions of polyenoic acids to prostanoid and prostaglandin endoperoxides and 2) examination of the chemistry of unsaturated hydroperoxy radicals like 12. Peroxy radical cyclizations of the type converting 12 to 13 have precedent in the literature, notably in Anet's work in the autooxidation of α -farnesene to a fully characterized 1,2-dioxolane hydroperoxide derivative.¹³ However, autooxidation of 9 or similar analogs would lead to mixtures of peroxy radicals, making systemic studies of radicals like 12 difficult. To get around this problem, Porter and co-workers¹⁴ exploited the precedented generation of peroxy radicals via radical abstraction of hydrogen from hydroperoxides¹⁵ to produce simple analogs of the peroxy radical 12. In their studies, the unsaturated hydroperoxides 19-23 (Scheme VI) were prepared from the solvolysis of the corresponding mesylates with alkaline hydrogen peroxide.¹⁶ These hydroperoxides were then treated with a source of t-butoxy radicals, di-t-butyl peroxalate (24) in oxygenated benzene to generate the corresponding hydroperoxy 1,2-dioxolanes in the case of 20-22 or 1,2-dioxane hydroperoxide in the case of 19, which were reduced with triphenylphosphine to the corresponding alcohols, 26-29, as in Scheme VI. Interestingly, 23 upon treatment with di-t-butyl peroxalate gave uncharacterized products which decomposed on silica gel at -20°C .

Scheme VI



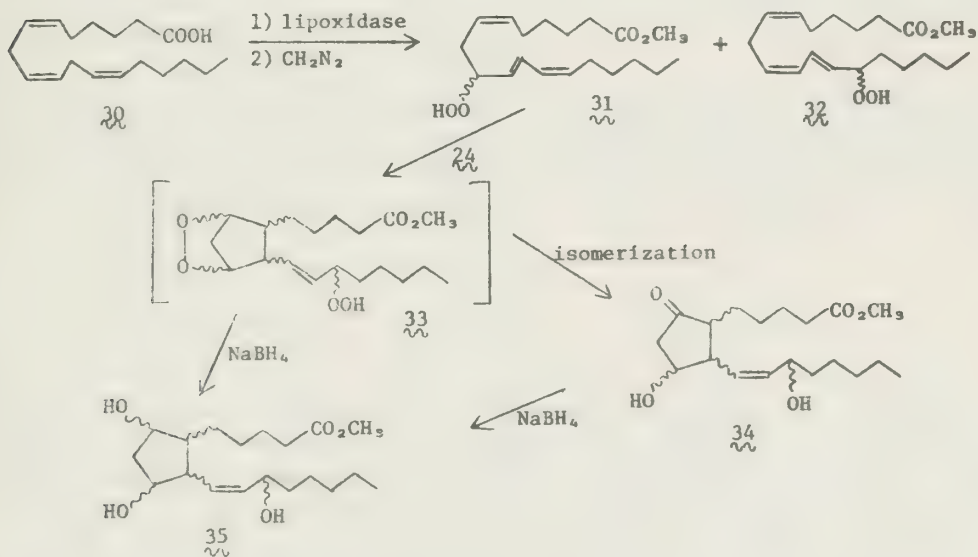
In light of these results, the authors have suggested that the peroxy radicals formed in the experiment in analogy with the known cyclizations of alkoxy and carbon radicals tend to cyclize to 5 membered rings via the mechanism in Scheme VII.

Scheme VII



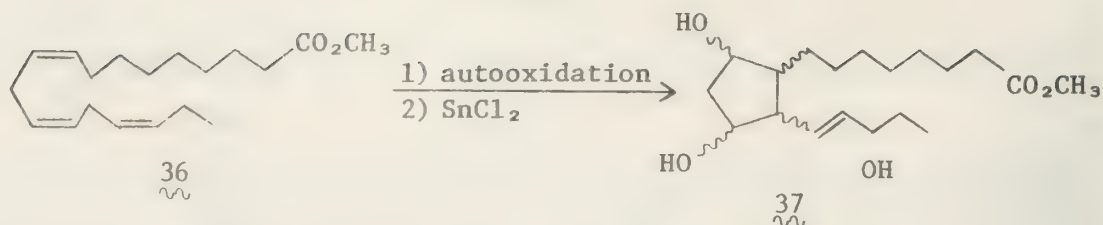
Porter and Pryor have also reported nonenzymatic cyclizations of more complex analogs of 12 (in Scheme IV). In Porter's work,^{17,20} all *cis*-6,9,12-octadecatrienoic acid (30) was incubated with the enzyme soybean lipoxidase followed by conversion of the crude hydroperoxy acids to their methyl esters with diazomethane to give 31 and 32. Treatment of 31 with di-*t*-butyl peroxalate (24) in oxygen-saturated benzene gave, upon reduction of the reaction product with sodium borohydride, a mixture of products. Two of these products, upon mass spectral analysis, appeared to have similar fragmentation patterns to authentic prostaglandin $\text{PGF}_{1\alpha}$ as in structure 35 (Scheme VIII). Porter suggested that the formation of 35 from 31 occurred via formation of the peroxy radical, followed by closure to the endoperoxide 33 which could have either 1) isomerized to a PGE_1 -like product 34 and underwent reduction to 35, or 2) directly underwent reduction to 35 as in Scheme VIII.

Scheme VIII



An additional study of Pryor¹⁸ has examined the products formed from stannous chloride reduction of autooxidation products of methyl linolenate 36 and has provided evidence (mass spectra, IR, UV, NMR) that some of these reduction products (Scheme IX) have the PGF_1 type structure 37. It is also worthwhile to note that the production of prostaglandins by autooxidation of 8,11,14-eicosatrienoic acid (7) has been reported.¹⁹

Scheme IX

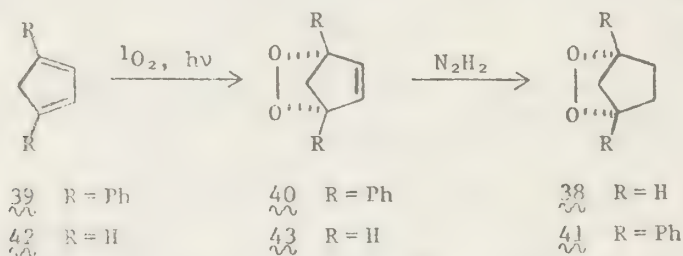


A Model of Prostaglandin Endoperoxide Chemical Synthesis and Chemistry: The 2,3-Dioxabicyclo[2.2.1]heptane System. The 2,3-dioxabicyclo[2.2.1]heptane system 38 is a key structural feature in the prostaglandin endoperoxides 1 - 6. Clearly, thorough understanding of the chemistry of 38 is essential not only in understanding the transformations of prostaglandin endoperoxides to prostaglandins and other metabolites but also in effecting a total chemical synthesis of the prostaglandin endoperoxides. Owing to the expected lability of 38 on the basis of the stabilities of the prostaglandin endoperoxides mentioned earlier, several new synthetic methods have been developed for dialkyl peroxides,²² 1,2-dioxolanes and 1,2-dioxanes, as well as 1,2-dioxepane and 1,2-dioxocane.²³ To date, successful syntheses of 38 and its derivatives have been reported by Adam,²⁴ Salomon²⁵ and Porter²⁶ and preliminary studies of their Lewis acid and thermally induced decompositions have been made.

Syntheses of 2,3-Dioxabicyclo[2.2.1]heptane (38) and Its Derivatives.

The first synthesis of a derivative of 38 was by Salomon,^{25b} for 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptane (41). In this synthesis, 39 was converted to 40 with singlet oxygen by standard procedures. Compound 40 was not isolated, but was reduced with the mild reducing agent diimide in situ to give 41 in 71% yield (Scheme X).

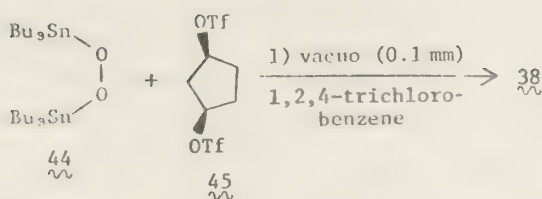
Scheme X



A synthesis of 38 in 30% yield from 1,3-cyclopentadiene (42) along similar lines was reported by Adam and co-workers. As the compound 43 has preceded instability,^{25b} it was necessary to perform the singlet oxygen addition-diimide (Scheme X) reduction steps at -78°C .²⁴

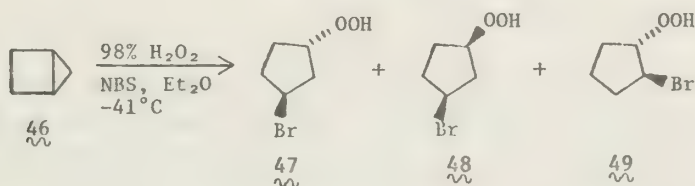
The first synthesis of 2,3-dioxabicyclo[2.2.1]heptane (38) was reported by Salomon and co-workers.^{25a} The scheme (Scheme XI) used a novel synthesis of cyclic organic peroxides developed by the authors featuring the action of bis-(tri-*n*-butyl tin)peroxide (44) on alkyl ditriflates at room temperature.^{23d} To avoid the disproportionation of 38 under the reaction conditions, the reaction between 44 and 45 was carried out under vacuo (0.1 mm) in 1,2,4-trichlorobenzene, with collection of the reaction product in a cold trap at -78°C to give 2,3-dioxabicyclo[2.2.1]heptane (38) in 13% yield.

Scheme XI



Another synthesis of 38, by Porter and co-workers, utilized the β -bromohydroperoxide-silver acetate procedure used to make the labile dioxetanes.^{21,26} The critical step in this synthesis was the formation of the β -bromohydroperoxide (Scheme XII) 47 or 48. This was achieved by the

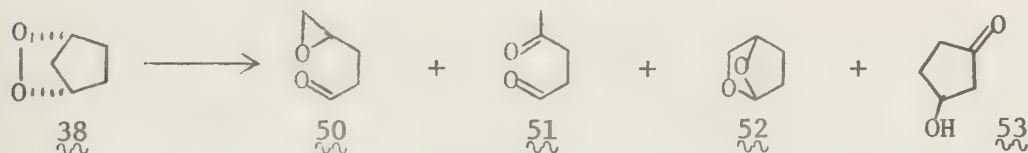
Scheme XII



action of 98% hydrogen peroxide and N-bromosuccinimide on bicyclopentane (46), to give 47, 48, and 49. Compounds 47 and 48 were the major products of the reaction (1:1 ratio), with 49 comprising less than 5% of the reaction mixture. Treatment of 47 with silver acetate in methylene chloride for 30 min gave 38 in quantitative yield. Compound 48 reacted with silver acetate much more slowly and after 6 hr, compound 38 and a product tentatively identified as a 3-acetoxycyclopentane hydroperoxide could be isolated. The differential reactivities of 47 and 48 were rationalized in terms of an assistance of bromide loss by the hydroperoxy group via an intramolecular S_N2 type transition state.²⁸

Thermally- and Lewis Acid-Induced Decompositions of 2,3-Dioxabicyclo [2.2.1]heptane (38). In a study of the thermal decompositions of 38, it was decomposed in a variety of solvents of differing dielectric constants at $73^\circ C$ or $43^\circ C$ to give products 50, 51, 52, and 53 (Scheme XIII). Under the

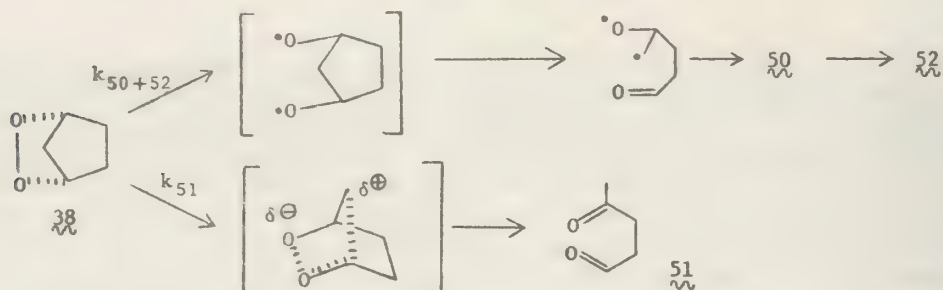
Scheme XIII



reaction conditions, 50, 51, and 53 did not undergo interconversion. However, the authors suggested 52 may have been an artifact of the decomposition of 50 as γ,δ -epoxyketones may give rise to compounds homologous to 52 at elevated temperatures. First order kinetics was verified for the disappearance of 38 over at least three half-lives as well as for the appearances of 50 and 51 in the solvents benzene D^6 , 2-butanone, acetonitrile D^3 , 1,2-dichloroethane D^4 . Three general results were obtained in the study: 1) the yields of 50-53 depended strongly on solvent; 2) the half-life of 38 varies widely with solvent, and 3) the rate constant for the formation of 51, k_{51} , increases with increasing solvent dielectric constant. To rationalize these results, Salomon postulated that the first

order decomposition of 38 was in fact a composite of two first processes as shown in Scheme XIV, one process being homolytic and only slightly dependent on solvent polarity and leading to 50 and ultimately 52 and the other process being mainly heterolytic and subject to solvent polarity and action of protic solvents. The unusually short half-lives observed for

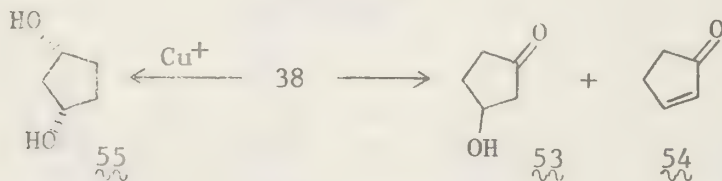
Scheme XIV



CD_3COOD and D_2O relative to solvents of similar dielectric constant were suggested to be due to protonation of the oxygen, promoting heterolysis. In addition, the formation of 53 with CD_3COOD and D_2O was rationalized in terms of the abilities of these solvents to abstract a proton from the bridgehead of 38.

Porter has recently examined reactions of endoperoxide 38 with Cu^+ and Cu^{+2} ion.²⁰ These studies are of interest in that when prostaglandin biosynthesis is permitted to occur in the presence of Cu^{+2} salts with or without added thiol, the yield of PGF products is significantly enhanced relative to the yield without added copper salts.²⁹ When 38 was treated with Cu^{+2} , 53 and 54 were formed. Compound 54 was shown to arise from 53 during the reaction and work-up conditions. In contrast, treatment of 38 with Cu^+ gave 55. It was noted that the decomposition of 38 in the absence of Cu^{+2} or Cu^+ was considerably slower. Porter has suggested that the earlier studies of the effects of Cu^{+2} on prostaglandin biosynthesis are clouded by the probable presence of Cu^+ in the reaction medium. Also of interest is Herz's suggestion that Fe^{+2} may bring about isomerizations of prostaglandin endoperoxides to PGE and PGF prostaglandins.³⁰

Scheme XV



BIBLIOGRAPHY

1. For recent reviews of prostaglandin endoperoxides, see: (a) B. Samuelsson in "Prostaglandin Research," P. Crabbe, ed., Academic Press, New York, N. Y., 1977, Chapter 2; (b) B. Samuelsson, E. Granström, K. Green, M. Hamberg, and S. Hammarström, *Ann. Rev. Biochem.*, 44, 669 (1975); (c) R. R. Gorman, *MTP Int. Rev. Sci.: Biochem.*, Ser., Two, in press.
2. B. Samuelsson, *J. Am. Chem. Soc.*, 87, 3011 (1965).
3. M. Hamberg and B. Samuelsson, *Proc. Nat. Acad. Sci. US.*, 70, 899.
4. D. H. Nugteren and E. Hazelhof, *Biochim. Biophys. Acta*, 326, 448 (1973).
5. M. Hamberg, J. Svensson, T. Wakabayashi, and B. Samuelsson, *Proc. Nat. Acad. Sci. USA*, 71, 345 (1974).

6. P. Needleman, M. Minkes and A. Raz, *Science*, 193, 163 (1976).
7. (a) R. R. Gorman, F. F. Sun, O. V. Miller, and R. A. Johnson, *Prostaglandins*, 13, 1043 (1977); (b) F. B. Ubatuba and S. Moncada, *Prostaglandins*, 13, 1055 (1977).
8. (a) B. Samuelsson, H. Granström, M. Hamberg, *Proceedings of the Nobel Symposium*, 2, 31-45 (1967); D. H. Nugteren, B. K. Beerhuis, and D. A. Van Dorp, *ibid.*, 2, 45-50 (1967).
9. B. Samuelsson, E. Granström, K. Grun, and M. Hambert, *Ann. N. Y. Acad. Sci.*, 180, 138 (1971).
10. T. Miyamoto, N. Ogino, S. Yamamoto, and O. Hayaishi, *J. Biol. Chem.*, 251, 2629 (1976).
11. For leading references on cyclooxygenase, prostacyclins, and a discussion of the physiological roles of prostaglandin, endoperoxides in conjunction with thromboxanes and prostacyclins, see: S. Senderoff, *University of Illinois Organic Chemistry Seminar Abstracts*, Spring 1978, p. 269.
12. (a) G. B. Kolata, *Science*, 190, 770; (b) M. Hamberg and B. Samuelsson, *Proc. Nat. Acad. Sci. USA*, 71, 3400 (1974).
13. E. F. Anet, *Aust. J. Chem.*, 22, 2403 (1969).
14. (a) M. O. Funk, R. Isaac, and N. A. Porter, *J. Am. Chem. Soc.*, 97, 1281 (1975); (b) N. A. Porter, M. O. Funk, D. Gilmore, R. Isaac, and J. Nixon, *J. Am. Chem. Soc.*, 98, 6000 (1976).
15. J. A. Howard, "Advances in Free Radical Chemistry," Vol. 4, G. H. Williams, ed., Academic Press, New York, N. Y., 1972, p. 49.
16. R. Hiatt, "Organic Peroxides," Vol. II, D. Swern, ed., Wiley Interscience, New York, N. Y., 1971, p. 1.
17. N. A. Porter and M. O. Funk, *J. Org. Chem.*, 40, 3614 (1975).
18. W. A. Pryor and J. P. Stanley, *J. Org. Chem.*, 40, 3615 (1975).
19. D. H. Nugteren, H. Vonkeman, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, 86, 1237 (1967).
20. N. A. Porter, J. R. Nixon, and D. J. Gilmore, in "Organic Free Radicals," ACS Symposium Series No. 69, American Chemical Society, Washington, D. C., 1978, Chapter 6.
21. (a) K. R. Kopecky, J. H. Van De Sande, and C. Mumford, *Can. J. Chem.*, 46, 25 (1968); (b) K. R. Kopecky, J. E. Filby, C. Mumford, P. A. Lockwood, and J. Y. Ding, *ibid.*, 53, 1103 (1975).
22. (a) M. F. Salomon, R. G. Salomon, and R. D. Gleim, *J. Org. Chem.*, 41, 3983 (1976); (b) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, 40, 1680 (1975); (c) R. A. Johnson, E. G. Nidy, and M. V. Merritt, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug. 29-Sept. 3, 1976, Abstract Orgn-107.
23. (a) A. J. Bloodworth and M. E. Loveitt, *J. Chem. Soc. Chem. Commun.*, 94 (1976); (b) W. Adam, A. Birke, C. Cádiz, S. Díaz, and A. Rodriguez, *J. Org. Chem.*, 43, 1155 (1978); (c) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975); (d) M. F. Salomon and R. G. Salomon, *J. Am. Chem. Soc.*, 99, 3500 (1977).
24. W. Adam and H. J. Eggelte, *J. Org. Chem.*, 42, 3987 (1977).
25. (a) R. G. Salomon and M. F. Salomon, *J. Am. Chem. Soc.*, 99, 3501 (1977); (b) D. J. Coughlin and R. G. Salomon, *J. Am. Chem. Soc.*, 99, 655 (1977).
26. N. A. Porter and D. W. Gilmore, *J. Am. Chem. Soc.*, 99, 3503 (1977).
27. R. G. Salomon, M. F. Salomon, and D. J. Coughlin, *J. Am. Chem. Soc.*, 100, 660 (1978).
28. P. G. Cookson, A. G. Davies, and B. P. Roberts, *J. Chem. Soc. Chem. Commun.*, 1022 (1976).
29. W. Lands, R. Lee, and W. Smith, *Ann. N. Y. Acad. Sci.*, 180, 107 (1971).
30. (a) J. A. Turner and W. Herz, *Experientia*, 33, 1133 (1977); (b) J. A. Turner and W. Herz, *J. Org. Chem.*, 42, 1895 (1977).

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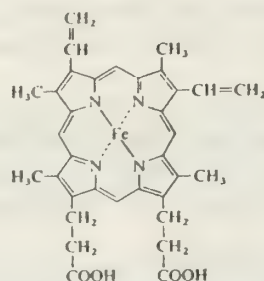
SYNTHETIC MODELS FOR HEMOGLOBIN AND MYOGLOBIN

Reported by Peter Senter

August 31, 1978

Hemoproteins are found in nearly all living organisms and perform a multitude of functions related to oxygen transfer and energy production. Among the important biological functions of hemoproteins are oxygen transport to tissue,^{1,2} catalytic oxidation of organic compounds,^{3,4} decomposition of hydrogen peroxide,⁵ and electron transport.⁶

Hemoproteins that function as oxygen carriers, e.g., myoglobin (Mb) and hemoglobin (Hb) are essential to the life of all vertebrates. These proteins also occur in some invertebrates, as well as in the root nodules of leguminous plants. The active site in Hb and Mb is a heme, protoporphyrin IX (1), tightly bound to a protein (globin) by about 80 hydrophobic interactions.⁷ In addition, an imidazole residue in the polypeptide chain coordinates to the iron. The species Mb is a monomer having only one heme group, while Hb is a tetramer composed of two identical α chains, two identical β chains, and four heme groups associated with each polypeptide chain.



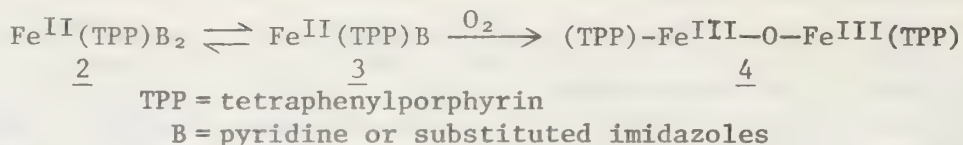
Fe-protoporphyrin IX (1)

In spite of many differences in the amino acid sequence,⁷ all Mb and Hb protein subunits have very similar tertiary structures consisting of eight helical regions designated by A-H. The proximal histidine, which is found in all Hb's and Mb's, invariably occurs as the eighth residue in the helical region F. The heme is wedged in a crevice between segments E and F. A rather open hydrophobic cavity is found on the distal (E) side where ligands such as O_2 , CO, CN^- , N_3^- and NO can bind to iron.

Of major importance to the activity of Hb and Mb is their ability to bind O_2 and CO reversibly. Simple heme porphyrins related in structure to 1 have been shown to reversibly bind CO, CN^- and several nitrogenous bases, but are irreversibly oxidized to corresponding hemins (Fe^{III}) when exposed to oxygen.^{1,3} Although a great deal has been learned about the nature of reversible O_2 binding through the studies of Hb and Mb, these studies have not yet resulted in a detailed molecular understanding of oxygen binding. In order to gain further understanding of reversible oxygen binding, considerable recent work has been directed towards the preparation of model compounds capable of mimicking this property of Hb and Mb.⁸⁻¹¹ The compounds synthesized are structurally designed to retard oxidation of the heme. Investigation of the structure and chemistry of heme- O_2 and heme-CO should give insight as to how oxygen and carbon monoxide affinities are controlled by the protein.

The main difficulty in preparing stable ferrous dioxygen complexes is fast irreversible oxidation of $Fe(II)$ to $Fe(III)$. When solutions of six coordinate iron(II) tetraphenylporphyrin complexes, 2, are exposed to oxygen, the μ -oxoferric dimer, 4, is formed with 3 as an intermediate.¹² The mechanism for the formation of the μ -oxo ferric dimer, 4, is believed to involve a bimolecular reaction between $Fe(TPP)O_2$ and either $Fe^{II}TPP$ or

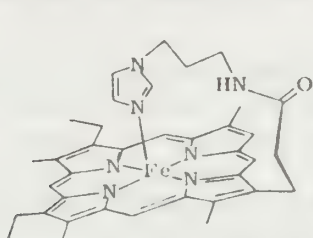
$\text{Fe}^{\text{II}}(\text{TPP})\text{B}$.^{9,13,14} Oxidation of iron- O_2 complexes are greatly accelerated in protic solvents.⁸



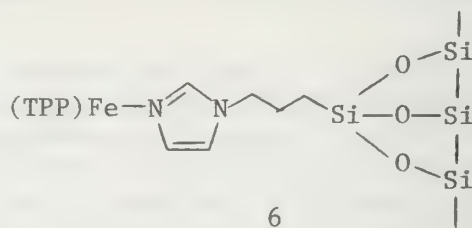
In designing models for Hb and Mb, it is necessary to prevent oxidation from taking place. This has been done in several ways. Hemes have been immobilized in solid matrices. This prevents the bimolecular reaction from taking place. The rate of oxidation has been greatly retarded by careful control of pertinent chemical and physical conditions. Heme models with distal side protection have been prepared in which the bimolecular reaction leading to oxidation is suppressed. Protection of heme models with carbon monoxide and the development of high speed experimental techniques have allowed direct observations of oxygen bound materials.

In the late 1950's, it was established by Wang that simple imidazole prophyrin complexes embedded in a polystyrene matrix were capable of reversibly binding oxygen and carbon monoxide.¹⁵ Wang demonstrated that the immobilized heme was air stable for several days.

Several years later, Traylor demonstrated that solid films of the heme 5 having an appended axial ligand was able to reversibly bind oxygen.¹⁶



5



6

Basolo and co-workers have recently studied oxygen uptake by a heme with the partial formula 6 fixed in a silica gel matrix.¹⁷ It was found that 6 bound oxygen weakly at 0° and much more strongly at lower temperatures without undergoing irreversible oxidation. Carbon monoxide was adsorbed strongly at 0° and was released at elevated temperatures.

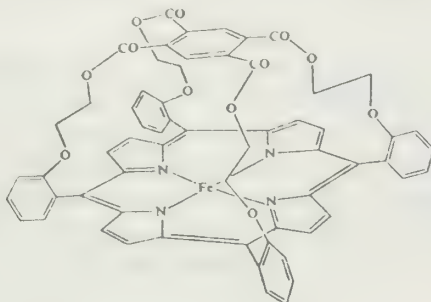
Bayer and Holzbach have reported that hemes covalently attached to water soluble polymers like polyethylene glycol bis (glycine ester) can undergo reversible oxygenation in aqueous solution.¹⁸

Reversible oxygenation of iron porphyrins in solution has been accomplished at low temperature.¹⁹ The stability of heme- O_2 complexes was greatest in polar aprotic solvents. It was found that reversible oxygenation was achieved with a wide variety of axial bases, including substituted imidazoles, pyridine, tert-butylamine, piperidine, and tetrahydrofuran.

A different approach to the kinetic stabilization of iron dioxygen complexes has been taken by Baldwin and by Collman. They reasoned that steric prevention of the bimolecular reaction leading to oxidation would prevent irreversible oxidation from taking place. This has been accom-

plished by the preparation of iron porphyrins having protective enclosures for binding oxygen on one side leaving the other side free to complex with an axial base.

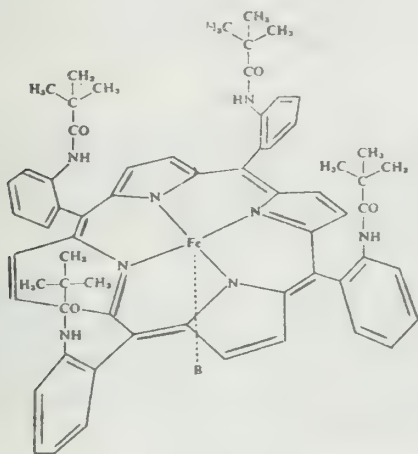
In an elegant synthesis, Baldwin prepared the cyclophane-type structure 7 which he termed a "capped porphyrin".²⁰



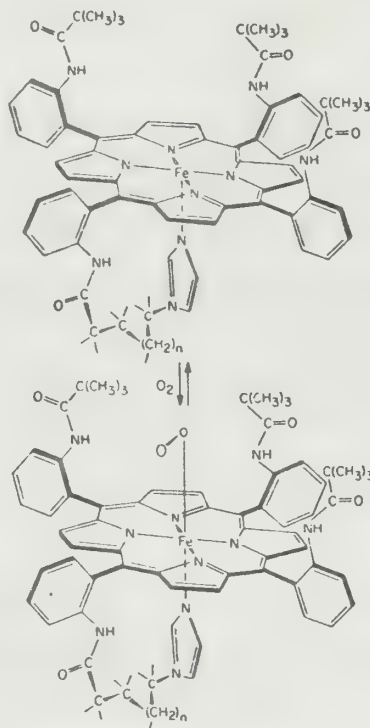
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The lifetime of 7 is several hours at 25°C with pyridine or 1-methylimidazole (N-MeIm) present as axial bases. Without these bases, irreversible oxidation resulting in the formation of the crystalline μ -oxo dimer took place rapidly.

Collman has circumvented the problem of irreversible oxidation of iron(II) dioxygen complexes by preparing sterically hindered porphyrins of the "picket fence" variety, 8 - 15.^{9,14,21}



- 8 B = N-MeIm
- 9 B = N-BuIm
- 10 B = THF
- 11 B = THT
- 12 B = 2-MeIm
- 13 B = Me₂Im



- 14 n = 0
- 15 n = 1

These picket fence porphyrins have steric bulk on one side of the porphyrin plane, but allow coordination of axial bases to the other side. Oxygen is capable of fitting inside the hydrophobic pocket (the fence) and complexing with the iron. Again, steric hindrance prevents oxidation from taking place.

It was found that when the four-coordinate iron picket fence complex was allowed to react with different substituted imidazoles, hexa-coordinate complexes, $\text{Fe}(\text{porphyrin})\text{B}_2$ could be obtained as crystalline solids.²² Electronic and NMR spectral observations showed that under one atmosphere of oxygen at 25°C in solution, these complexes completely oxygenated. In solution, these dioxygen complexes were shown to have half lives for conversion to oxidized compounds of two to three months at room temperature.

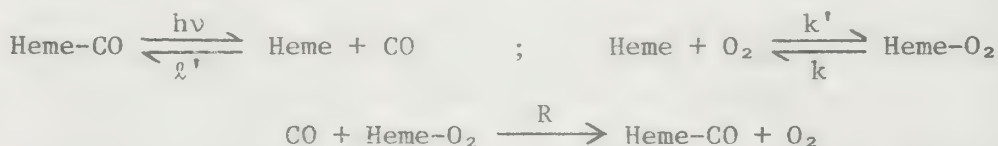
Thus far, the O_2 adducts of compounds 8-15 have been isolated in crystalline form. The structures of $\underline{8}\text{-O}_2$ ²³ and $\underline{12}\text{-O}_2$ ²⁴ have been determined by X-ray diffraction. Both complexes were shown to bind oxygen in an end-on manner with a bent Fe-O-O bond. Since $\underline{8}\text{-O}_2$ and oxygenated hemoproteins have similar spectral data, it seems likely that Hb and Mb bind oxygen in an end-on manner as proposed by Pauling²⁵ rather than in an edge bound manner as proposed by Griffith.²⁶

The dioxygen ir stretching frequency of $\underline{8}\text{-O}_2$ was observed at 1159 cm^{-1} .²⁷ This frequency did not vary significantly with changes in the macrocyclic ligand or when Co^{II} was substituted for Fe^{II} . Since the ir stretching frequency of $\underline{8}\text{-O}_2$ is very close to that observed for superoxide (1145 cm^{-1}), the superoxide formalism has been applied to these end-on complexes.

The CO stretching frequency in $\underline{8}\text{-CO}$ is higher than that observed for hemoproteins.²⁷ X-ray diffraction studies have shown that Hb-CO and Mb-CO bonds are not linear.²⁸ Collman has hypothesized that a major function of the protein is to provide steric bulk to the ligand binding site so as to distort the normally linear Fe-CO bond. This results in a lower carbon monoxide affinity.

Thermodynamic studies of oxygen binding to 8 in the solid state give values of ΔH° , ΔS° and $\text{P}_{1/2}$ (the oxygen pressure at half saturation) very similar to those observed for Mb.²⁹ This suggests that the Mb apoprotein does not contribute significantly to the binding of oxygen.

Carbon monoxide protection of heme models has proved to be effective in preventing irreversible oxidation. Traylor has shown that solutions of heme-CO are stable even in the presence of oxygen.³⁰ Flash photolysis of heme-CO complexes cleaves off the CO, and if carbon monoxide and oxygen are present in solution, the following reactions occur:



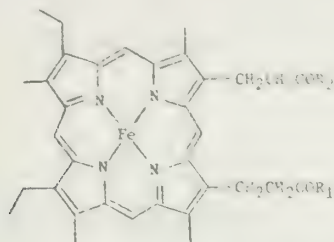
The reaction is followed spectrophotometrically, and under carefully controlled conditions, the following equation is valid:³¹

$$\frac{1}{R} = \frac{1}{k} + \frac{k'(O_2)}{k\ell'(CO)}$$

R and ℓ' are measured directly, and k and k' are determined graphically.

Using flash photolysis, Traylor has developed a method of determining the extent to which heme porphyrins are ligated at a given pH.³² While the

four coordinate species mesoheme-dimethylester (16) reacts with CO at a rate independent of pH, $k' = 4 \cdot 10^5$ l/mole sec, compounds 17 and 18 react at a much slower rate ($k' = 1 \cdot 10^7$ l/mole sec) at high pH.



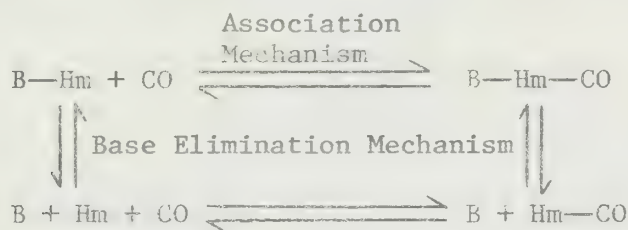
16: $R_1 = OCH_3$, $R_2 = OCH_3$

17: $R_1 = NH(CH_2)_3 \text{N} \begin{array}{c} \diagup \\ \diagdown \end{array}$, $R_2 = OCH_3$

18: $R_1 = O(CH_2)_3 \text{N} \begin{array}{c} \diagup \\ \diagdown \end{array}$, $R_2 = OCH_3$

At high pH, 17 and 18 are five coordinate. At low pH, where the bases are protonated and not coordinated to the iron, 17 and 18 display CO combination rates equivalent to 16. The fact that k' for 17 and 18 at low pH is forty times greater than that at high pH suggests that carbon monoxide combination is taking place by two different mechanisms.^{33,34} These two mechanisms for CO binding are shown in Figure 1.

Figure 1



Hm = iron(II)porphyrin

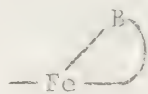
Flash photolysis of B-Hm-CO produces B-Hm. At high pH, BHm simply captures CO via the associative mechanism with $k' = 1 \cdot 10^7$ l/mole sec. At low pH, B rapidly dissociates, becomes protonated, and reacts by the faster process in which $k' = 4 \cdot 10^6$ l/mole sec, a rate typical of four coordinate hemes. This is the base elimination mechanism. Traylor has shown that the change from the direct association mechanism to the base elimination mechanism can be achieved at pH 7.3 simply by introduction of steric hindrance into the proximal base.

There are several indications that the base elimination mechanism may be possible in hemoproteins. It has recently been reported that Mb has a pH-rate profile for reaction with CO similar to that reported for 17.³⁴

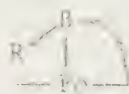
One of the most significant properties of Hb is its ability to cooperatively bind oxygen. Binding of one molecule of oxygen to a subunit site makes binding at other sites easier. Thus, at low oxygen pressures, Hb has a low oxygen affinity, but at high oxygen pressures, Hb has a high oxygen affinity. In exercising muscle where the oxygen concentration is low, Hb gives oxygen to Mb, which serves as an oxygen reservoir.

Several general mechanisms have been proposed to explain Hb cooperativity.^{7,35,36} In the most detailed mechanism, Perutz^{7,37} and Hoard³⁸ have suggested that in low affinity deoxy Hb, the T-state, the high spin iron is forced out of the heme plane by as much as 0.75 \AA . When oxygen binds, the iron with its attached imidazole is pulled back into the plane of the heme. This movement causes conformational changes which alter the reactivity of adjacent hemes by stabilizing the high affinity form of Hb, the R-state.

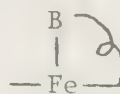
It has been of interest to create such deformations in heme model compounds and study their effect on oxygen and carbon monoxide binding. Traylor has done this by introducing steric effects into the chelated heme 17 in order to determine if change in proximal base strain would result in T-state Hb behavior.³⁰ Strain has been introduced in three ways:



ring strain

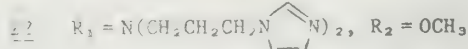
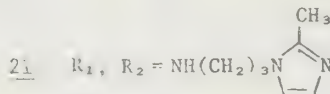
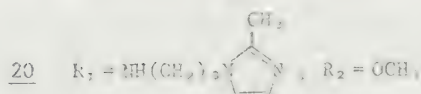
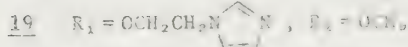
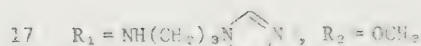
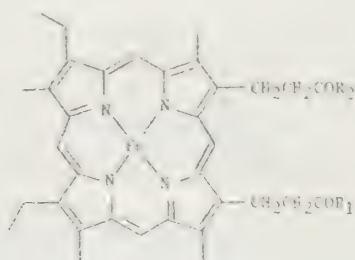


face strain



springboard strain

Ring strain has been introduced by reducing the ring size of the chelating chain (19). Face strain has been introduced by use of a bulky axial imidazole (20 and 21). Another way to create strain is to introduce steric bulk in the chelating chain. This is called springboard strain as it tends to spring open the heme-imidazole connection (22).



Upon introduction of proximal strain into chelated hemes, both oxygen and carbon monoxide binding constants are reduced. This is consistent with the postulate that out of plane forces on the heme iron reduce binding affinity.^{7,38} Traylor has concluded that 19, 20, and 22 are models for the Hb T-state. These compounds react with CO by the base elimination mechanism. Preliminary evidence suggests that reaction with oxygen takes place by the association mechanism.

Table 1 shows the rates of carbon monoxide reaction (k') with Hb α chains; legoglobin and chironimus Hb are comparable to the rates observed for the unstrained heme model 17. It is noteworthy that proximal strain and distal hindrance have little effect on the O_2 binding rate, k' . This is consistent with a proposed charge transfer type of early transition state for O_2 binding, in which perhaps an O_2Fe^+ pair forms at some distance, thus reducing the steric effects upon k' .⁴³

Collman has recently reported studies of oxygen binding to both iron and cobalt picket fence porphyrins having hindered and unhindered imidazole axial bases.^{21,44} It was found that iron porphyrins with unhindered axial bases displayed little variance in $P_{1/2}$, ΔH° and ΔS° . These values compared very well with those observed for R-state hemoproteins. In addition, $P_{1/2}$, ΔH° and ΔS° of cobalt picket fence porphyrins and CoMb were very similar. It was concluded that special interactions between the

Table 1. Proposed Effects of Proximal Strain and Distal Steric Hindrance on the Kinetics of Heme Reactions with CO and O₂.

Heme	Proximal Strain	Distal Hindrance	k'	k''	ref
17	none	none	$1.1 \cdot 10^7$	$2 \cdot 10^7$	34
α chain	none	little	$4 \cdot 10^6$	$5 \cdot 10^7$	39
legoglobin	none	little	$1.3 \cdot 10^7$	10^8	40
myoglobin	none	large	$5 \cdot 10^5$	$1.5 \cdot 10^7$	41
22	medium	none	$4.8 \cdot 10^7$	$4.7 \cdot 10^7$	34
20	large	none	$1.2 \cdot 10^8$	—	34
chironimus Hb	medium	none	$3 \cdot 10^7$	$3 \cdot 10^8$	42

protein and the bound oxygen are not needed to explain the oxygen affinities in these hemoproteins. As previously mentioned, this is not the case for carbon monoxide affinity.

Models for T-state Hb were constructed by introducing steric hindrance into the axial base. The 2-methyl group of Me₂Im provides hindrance of movement of this axial base towards the porphyrin upon oxygenation. It was found that picket fence porphyrins with Me₂Im as the axial base had values for $P_{1/2}$, ΔH° , and ΔS° which were similar to those observed for T-state hemoproteins.

The R- and T-state heme models presented so far have been shown to mimic the R- and T-state Hb's kinetically and thermodynamically. The restraint presumed to be present in the T form of Hb and CoHb have been well modelled by Traylor's and Collman's porphyrin systems, and the results obtained have provided evidence on a molecular level that the Hoard-Perutz mechanism is viable.

In a recent study the oxygen binding to solid state picket fence porphyrins was recorded at different oxygen pressures.⁴⁵ It was found that 12 and 13 actually showed cooperative binding. The oxygen uptake curves for 12 and Hb were strikingly similar. The reason for the cooperative binding observed for 12 and 13 was thought to be due to changes in molecular dimensions occurring as the solid oxygenates. Presumably, strain is induced, and a conformational change in the solid enhances the oxygen affinity of the remaining deoxy sites.

However, 8⁴⁵ and 12-EtOH⁴⁴ bound oxygen without cooperative interaction. Assuming that 12-EtOH and 12 are structurally and chemically similar, it appears that the observed cooperativity for solid state porphyrins arises from complex intermolecular interactions, and not just by a change in axial base ligation.

Recent technological advances have made it possible to obtain extended X-ray absorption fine structure (EXAFS) spectra of dilute solutions of metalloproteins.⁴⁶ The absorption of X-rays by a metal atom creates photoelectrons which when backscattered by the ligands modulate the X-ray absorption. Using EXAFS, it is possible to measure bond lengths in the vicinity of absorbing atoms to accuracies of approximately 0.01 Å. EXAFS measurements have very recently been made on Hb, HbO₂, 8, and 8-O₂.⁴⁷

Table 2. EXAFS Fe-Np Distances

Compound	Fe-Np	X-Ray Diffraction
Hb	2.055 ± 0.01	
8	2.055 ± 0.01	2.069 ± 0.013
HbO ₂	1.986 ± 0.01	
8-O ₂	1.979 ± 0.01	1.979 ± 0.01^{23}

The Fe-Np term represents the average distance between the iron and the nitrogens in the heme plane. The Hoard-Perutz proposal was based on an observed Fe-Np distance averaging 2.074 \AA in three ferric porphyrins.^{6,38} Hoard estimated by analogy with ionic crystals that the ferrous Fe-Np distances should be longer by as much as 0.12 \AA suggesting an Fe-Np distance of 2.19 \AA .

It can be seen that the Fe-Np distance determined by EXAFS is significantly shorter than that estimated by Hoard. Eisenberger and co-workers claim that the estimated Fe-Np distances used by Hoard and Perutz are inapplicable as it is incorrect to assume that ionic radii of ferric and ferrous crystals apply to heme compounds.

The EXAFS distances are in excellent agreement with the recent X-ray diffraction work by Collman. For a porphyrin radius of 2.045 \AA ,⁴⁷ the observed Fe-Np value of $2.055 \pm 0.01 \text{ \AA}$ for Hb and 8 indicates that the iron is $0.2 +0.1/-0.2 \text{ \AA}$ out of the porphyrin plane. These results indicate that the Fe is not forced out of the porphyrin plane by long Fe-Np bonds as was proposed by Hoard and Perutz.

An iron motion of 0.3 \AA is no larger than several changes in porphyrin structure observed during oxygenation. Karplus and Gelin have suggested that distortions in the heme occur upon oxygenation which eventually cause the heme to tilt in a direction calculated to produce the maximum interaction with the globin.⁴⁸ Eisenberger and co-workers claim that the distortions associated with oxygenation are transmitted through general changes of the heme rather than being localized in a simple driven motion of the iron atom.⁴⁷

It is therefore likely that the reported similarities between the T-state heme models and T-state Hb are not associated with non-planarity of the penta-coordinated iron porphyrin. More investigation into the precise nature of T-state Hb is needed.

Heme models have contributed a great deal to what is known about hemoproteins. The synthesis and structural investigation of heme-O₂ complexes has clarified the nature of the iron oxygen bond in Hb and Mb. The role played by the protein in the prevention of oxidation and inhibition of carbon monoxide binding is now well understood. Two mechanisms for ligand binding to hemoproteins have resulted from model work. Heme models have furthered our understanding of both R- and T-state hemoproteins. It seems evident that investigations into the activity of Hb and Mb will continue to rely on information obtained from heme models.

BIBLIOGRAPHY

1. F. Antonini and M. Brunori, "Hemoglobin and Myoglobin and Their Reactions with Ligands", North Holland Publishing Co., Amsterdam, 1971.
2. J. M. Fifkind, *Inorg. Biochem.*, 2, 832 (1973).
3. O. Hayaishi, ed., "Molecular Mechanisms of Oxygen Activation", Academic Press, New York, 1974.
4. R. Lemberg and J. Barrett, "The Cytochromes", Academic Press, New York, 1973.
5. P. Nicholls and G. R. Schonbaum, in "The Enzymes", P. D. Boyer, H. Lardy, and K. Myrback, eds., 2nd ed., Vol. 8, Academic Press, New York, 1963.
6. J. L. Hoard in "Porphyrins and Metalloporphyrins", K. M. Smith, ed., Elsevier, Amsterdam, 1975.
7. M. F. Perutz, *Brit. Med. Bull.*, 32, 193 (1976).
8. T. G. Traylor, *Bioorg. Chem.*, 4, 437 (1978).
9. J. P. Collman, *Acc. Chem. Res.*, 10, 265 (1977).
10. J. W. Buchler, *Angew. Chem. Int. Ed. Engl.*, 17, 407 (1978).
11. F. Basolo, B. M. Hoffman, and J. A. Ibers, *Acc. Chem. Res.*, 8, 384 (1975).
12. A. B. Hoffman, D. M. Collins, V. W. Day, E. B. Fleischer, T. S. Strivasta, and J. L. Hoard, *J. Am. Chem. Soc.*, 94, 3620 (1972).
13. G. S. Hammond and C. H. S. Wu, *Advan. Chem. Ser.*, 77, 186 (1968).
14. J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lane, and W. T. Robinson, *J. Am. Chem. Soc.*, 97, 1427 (1975).
15. J. H. Wang, *J. Am. Chem. Soc.*, 80, 3168 (1958).
16. C. K. Chang and T. G. Traylor, *Proc. Natl. Acad. Sci., U.S.A.*, 70, 2647 (1973).
17. O. Leal, D. L. Anderson, R. G. Bowman, F. Basolo, and R. L. Burwell, *J. Am. Chem. Soc.*, 97, 5125 (1975).
18. E. Bayer and G. Holzbach, *Angew. Chem. Int. Ed. Engl.*, 16, 117 (1977).
19. (a) C. K. Chang and T. G. Traylor, *J. Am. Chem. Soc.*, 93, 5810 (1973); (b) C. K. Chang and T. G. Traylor, *ibid.*, 95, 8476 (1973); (c) W. S. Brinigar and C. K. Chang, *ibid.*, 96, 5595 (1974); (d) C. K. Chang and T. G. Traylor, *ibid.*, 95, 8477 (1973); (e) W. S. Brinigar, C. K. Chang, J. Geibel, and T. G. Traylor, *ibid.*, 96, 5597 (1974); (f) G. C. Wagner and R. J. Kassner, *ibid.*, 96, 5593 (1974); (g) J. E. Baldwin, R. L. Dyer, J. Huff, and C. J. Wilkerson, *ibid.*, 96, 5600 (1974); (h) D. L. Anderson, C. J. Weschler, and F. Basolo, *ibid.*, 96, 5599 (1974).
20. (a) J. Almog, J. E. Baldwin, and J. Huff, *J. Am. Chem. Soc.*, 97, 226 (1975); (b) J. Almog, J. E. Baldwin, R. L. Dyer, and M. Peters, *ibid.*, 97, 227 (1975).
21. J. P. Collman, J. I. Brauman, K. M. Doxsee, T. R. Halbert, and K. S. Suslick, *Proc. Natl. Acad. Sci., U.S.A.*, 75, 564 (1978).
22. (a) J. P. Collman, R. R. Gague, C. A. Reed, T. R. Halbert, G. Lang, and W. T. Robinson, *J. Am. Chem. Soc.*, 97, 1427 (1975); (b) J. P. Collman, R. R. Gauge, T. R. Halbert, J. C. Marchon, and C. A. Reed, *ibid.*, 95, 7868 (1973).
23. J. P. Collman, R. R. Gauge, C. A. Reed, W. T. Robinson, and G. A. Rodley, *Proc. Natl. Acad. Sci., U.S.A.*, 71, 1326 (1974); G. B. Jameson, G. A. Rodley, W. T. Robinson, R. R. Gagne, C. A. Reed, and J. P. Collman, *Inorg. Chem.*, 17, 850 (1978).
24. G. B. Jameson, F. S. Molinaro, J. A. Ibers, J. P. Collman, J. I. Brauman, E. Rose, and K. S. Suslick, *J. Am. Chem. Soc.*, submitted for publication.
25. L. Pauling, *Nature*, 203, 182 (1964).
26. J. S. Griffith, *Proc. R. Soc. London, Ser. A.*, 235, 23 (1956).
27. J. P. Collman, J. I. Brauman, T. R. Halbert, and K. S. Suslick, *Proc. Natl. Acad. Sci., U.S.A.*, 73, 3333 (1976).
28. S. M. Peng and J. A. Ibers, *J. Am. Chem. Soc.*, 98, 8032 (1976).

29. J. P. Collman, J. I. Brauman, and K. S. Suslick, *J. Am. Chem. Soc.*, 97, 7185 (1975).
30. (a) C. K. Chang and T. G. Traylor, *Proc., Natl. Acad. Sci., U.S.A.*, 72, 1166 (1975); (b) C. K. Chang and T. G. Traylor, *Biochem. Biophys. Res. Commun.*, 62, 729 (1975).
31. R. W. Noble, Q. H. Gibson, M. Brunori, E. Antonini, and J. Wyman, *J. Biol. Chem.*, 244, 3905 (1969).
32. J. Geibel, C. K. Chang, and T. G. Traylor, *J. Am. Chem. Soc.*, 97, 5924 (1975).
33. J. Cannon, J. Geibel, M. Whipple, and T. G. Traylor, *J. Am. Chem. Soc.*, 98, 3395 (1976).
34. J. Geibel, J. Cannon, D. Cambell, and T. G. Traylor, *J. Am. Chem. Soc.*, 100, 3575 (1978).
35. D. E. Koshland, G. Menethy, and D. Filmer, *Biochemistry*, 5, 365 (1966).
36. J. Monod, J. Wyman, and J. P. Changeux, *J. Mol. Biol.*, 12, 88 (1965).
37. M. F. Perutz, *Nature*, 228, 726 (1970).
38. J. L. Hoard, *Science*, 174, 1295 (1971).
39. M. Brunori and T. M. Schuster, *J. Biol. Chem.*, 244, 4046 (1969).
40. T. Imamura, A. Riggs, and Q. H. Gibson, *J. Biol. Chem.*, 247, 521 (1972).
41. See ref. 1, p. 220.
42. G. Amieoni, E. Antonini, M. Brunori, H. Formanek, and R. Huber, *Eur. J. Biochem.*, 31, 52 (1972).
43. A. Szabo, *Proc. Natl. Acad. Sci., U.S.A.*, 75, 2108 (1978).
44. J. P. Collman, J. I. Brauman, K. M. Doxsee, T. R. Halbert, S. E. Hayes, and K. S. Suslick, *J. Am. Chem. Soc.*, 100, 276 (1978).
45. J. P. Collman, J. I. Brauman, E. Rose, and K. S. Suslick, *Proc. Natl. Acad. Sci., U.S.A.*, 75, 1052 (1978).
46. R. G. Shulman, P. Eisenberger, and B. M. Kincaid, *Ann. Rev. Biophys. Bioeng.*, 559 (1978).
47. P. Eisenberger, R. G. Shulman, B. M. Kincaid, G. S. Brown, and S. Ogawa, *Nature*, 274, 30 (1978).
48. B. R. Gelin and M. Karplus, *Proc. Natl. Acad. Sci., U.S.A.*, 74, 801 (1977).

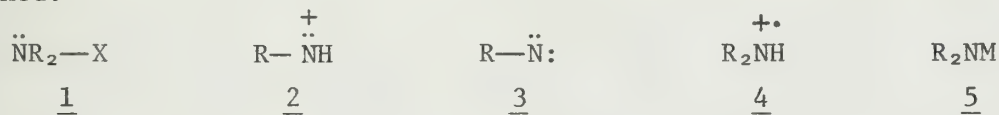
ELECTROPHILIC AMINATION REAGENTS

Reported by Michael W. Robertson

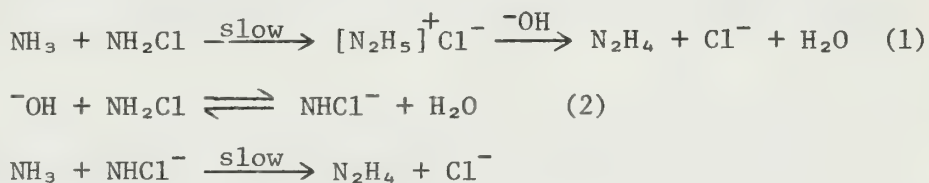
September 7, 1978

The vast majority of synthetically useful reactions involving the introduction of the amino moiety, $-NR_2$ ($R=H$, alkyl, aryl), into a molecule proceed through the reaction of a nucleophilic nitrogen species with an appropriate electrophile.¹ The reaction of an electrophilic nitrogen function with a nucleophilic species has been rather limited to date. The increasing use of such reagents in synthesis suggests this alternative to amination is now viable. The purpose of this report is to summarize the mechanistic aspects and synthetic applications of the major electrophilic amination species.

Five types of formal reagents or reactive intermediates represented by 1-5 have been studied. The broadest class of compounds are those generalized as the heteroatom substituted amines 1. A second electrophilic aminating species is the proposed highly reactive nitrenium ions 2. The third class of electron deficient nitrogen species are the nitrenes 4. The cationic amino radicals 3 have been reputed to be electrophilic, also. The reactions of some organometallic oxy-amination reagents, 5, can lead to aminations although the mechanisms of these processes are not well defined.



Heteroatom Substituted Amines, 1. The classical reagents of general structure 1 are the halamines of which chloramine has received the greatest scrutiny.² The Raschig synthesis of hydrazine from ammonia and chloramine illustrates the mechanism of this general class of reagents.³ It has been proposed by Yagil in a detailed kinetic study that a bimolecular nucleophilic attack of ammonia on chloramine proceeds by a base independent path (1) and a base catalyzed route (2).⁴



Evidence supporting the proposed base independent mechanism is derived primarily from the observed first order kinetics of both ammonia and chloramine in the pH range 10-14. Moreover, it was observed that reaction rates increased with increased N-methyl substitution on the substrate amines (increased nucleophilicity) with a concurrent rate decrease for N-methyl substitution on the N-chloramine (decreased electrophilicity).

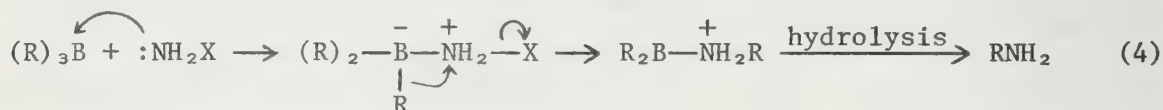
At a pH greater than 14, a rapid preequilibrium was postulated before the rate limiting step to account for the substantial rate acceleration observed. Once again the reaction exhibited second order kinetics, first order with respect to both amine and chloramine. In effect, the increased rates observed for the base catalyzed reaction relative to the base independent has been rationalized by an increased N-Cl bond polarization in chloramide anion relative to chloramine, presumably leading to a more favorable leaving group situation in the chloramide anion. Several alternatives to the proposed mechanism were considered. The possibility of a

preequilibrium involving chloramide dissociation into the imidogen nitrene and chloride ion in the rate determining step, initially proposed by Audrieth,⁵ was excluded due to the necessity of a zero order rate expression for ammonia. Moreover, the existence of a rapid equilibrium to form the reactive nitrene intermediate was expelled due to the lack of a chloride common ion rate depression. Thus, the data has been taken to suggest an S_N2 mechanism, operative by either base catalysis or no catalysis, depending on the pH of the reaction solution.

Amination has been observed with the N-halamines for a wide range of nucleophiles in good yields. As representative examples, alkoxides, secondary amines, Grignards, sulfides and oximes are aminated by chloramine to produce O-alkylhydroxylamines,⁹ hydrazines,^{4b} primary amines,¹⁰ amino-sulfonium salts⁸ and diazoalkanes.¹³ Carbanions derived from organozinc, organolithium and organopotassium reagents have been reported to be aminated by halamines as well.^{14,15} It is of interest to note two aspects of the amination of Grignard reagents by halamines. First, the yields of amines decrease upon going from chloramine to bromamine and secondly, aryl Grignard reagents were found to give very low yields. A competing halogen metal exchange reaction (3) was invoked to account for these observations.



Moreover, the increased basicity of N in N-bromamines is taken to reflect a less favorable site for nucleophilic attack. The dual character of halamine as halogenation species as well as an aminating reagent is also illustrated by Equation 3. Another route for carbon amination by NH₂X reagents is the synthesis of amines from organoboranes (4).¹⁶ This reaction has been found to be highly stereoselective with yields generally between 50-60%. A mechanistic study of this reaction^{16b} concluded that the reaction mechanism is similar to that proposed for the reaction between hydrogen peroxide and organoboranes in a basic media.

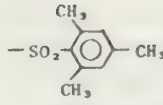
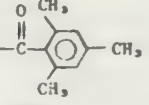
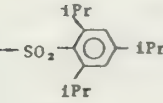
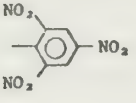
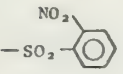
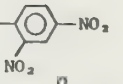
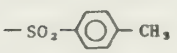
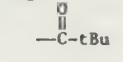


The N-halamines are readily available from the action of molecular halogen on trimethylsilyl amines in yields of 40-90%^{17a} as well as the oxidation of amines by the hypohalite series.^{17b} These compounds display low solubilities in the common organic solvents but are readily soluble in methanol and water. The toxicity and potentially explosive nature of these reagents requires the utmost caution in their handling.

Recently a group of hydroxylamine derived electrophilic amination reagents has been investigated.¹⁸ Substitution at oxygen provides useful sulfonate, benzoate and phenoxide derivatives listed in Table 2.

The simplest example is hydroxylamine-O-sulfonic acid, 6, which has now received nearly as much attention as the halamines.¹⁹ Mechanistically²⁴ and synthetically,²⁵ these two reagents appear equivalent with 6, possessing an advantage in ease of handling. Reagents 7-14 have several advantages over the classical reagents as summarized by a recent review.¹⁸ In essence, use of 7-14 relative to chloramine and 6 provides high solubility in common organic solvents, simple synthetic procedures, extremely mild reaction conditions, high yields and a wide scope of applicability.

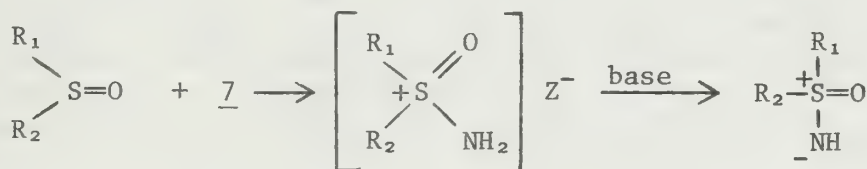
Table 1. Electrophilic Amination Reagents NH_2OZ

entry	Z	ref	entry	Z	ref
<u>7</u>		<u>20</u>	<u>11</u>		<u>21,22</u>
<u>8</u>		<u>20</u>	<u>12</u>		<u>20,23</u>
<u>9</u>		<u>20</u>	<u>13</u>		<u>20,23</u>
<u>10</u>		<u>21</u>	<u>14</u>		<u>22</u>

A recent mechanistic study of the reaction of 13 with various nucleophiles has shown a second order rate law, first order in each reactant.²⁶ The mechanism is considered to be a direct $\text{S}_{\text{N}}2$ displacement via a trigonal bipyramidal transition state.

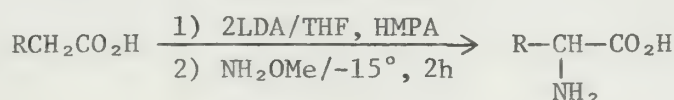
As with the classical reagents, 7-14 react with a wide range of nucleophiles. For example, the reaction of 7 with 2 amines, phosphines, and sulfides affords dialkyl hydrazines,²¹ aminophosphosium salts¹⁸ and aminosulfonium salts,²⁸ the last of which provides a convenient entry into sulfilimine synthesis. Several notable features of the use of reagents 7-14 deserve mention. First, the yields obtained in these reactions are generally superior to those of the classical reagents. Secondly, selectivity between aliphatic and aromatic tertiary amines is synthetically useful as observed in the 54% yield of the monoaminated product from nicotine.³³ Finally, oxime formation is not a significant side reaction as observed by the excellent yields of N-aminated ketoamines.^{29,30} This last point is of special significance owing to the reported preference of oxime formation by the reaction of 6 with certain amino-aldehydes.¹⁸

Reagent 7 has proven to be a versatile reagent in the synthesis of sulfoximines from sulfoxides.²⁸



For example, Johnson has reported the synthesis of optically active sulfoximes from optically active sulfoxides and 7 in good yields and high enantiomeric purity.³⁴ Other synthetic uses of this mild reagent include desulfurization of dithioacetals, dithioketals, and thioketones to afford ketones and aldehydes in generally good yields.^{35,36}

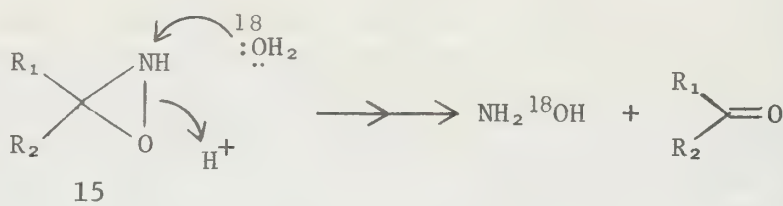
Amination of formal carbanions by hydroxylamine derivatives is of considerable interest. The most striking example is that of Yamada in the one step synthesis of racemic α -amino acids in ca. 50% yields as shown:³⁷



Although the amination of carbanions has not been systematically studied by the use of electrophilic reagents 7-14, scattered examples have been reported. Sheradsky obtained ca. 50% yield for the reaction of sodium diethylphenylmalonate with 13.³⁸ Recently, Scopes has achieved an enolate amination by a one step reaction of 7 with the sodium hydride derived anion of methyl diethylphosphonacetate in 39-47% yield, a process that had previously been accomplished in five steps with an overall yield of 18%.³⁹ Finally, organoboranes have been shown to react with reagent 7 to afford primary amines under mild conditions.^{16c}

The synthesis of reagents 7-14 has been most conveniently accomplished by the acid hydrolysis of alkylated hydroxycarbamates and the acid hydrolysis of alkylated ethyl acetohydroxamates in respectable yields.¹⁸

A final example of a heteroatom substituted amine functioning as an aminating reagent is the oxaziridine 15, although the synthetic applications of this type of electrophilic reagent has been rather limited. A partial mechanistic investigation employing ¹⁸O isotopic labelling in the acid hydrolysis of 15 (R₁, R₂ = 3,3-pentamethylene) was taken to suggest an electrophilic amination pathway was probable owing to a 52% incorporation of ¹⁸O into the hydroxylamine product.²⁵

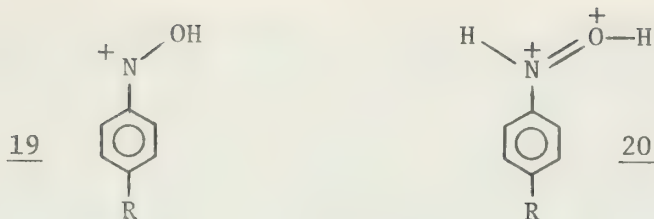


Aminations by Formal Nitrenium Ions, 2. A second electrophilic species which can lead to amination is the intermediate nitrenium ions, 2. There has been a lively debate in the literature as to the existence of this species. Gassman and co-workers are the principle proponents of solvolytically induced formation of intermediate nitrenium ions⁴² whereas Edwards et al. suggest that this species is not actually formed.⁴³

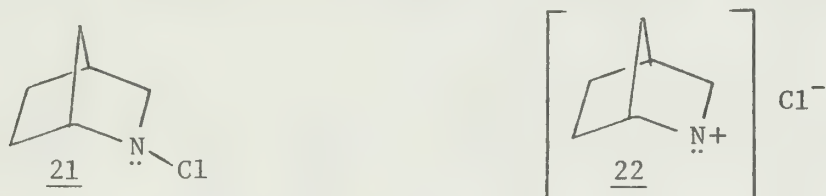
The existence of aryl nitrenium ions has been unambiguously determined by electrochemical anodic oxidation of various substituted diarylamines.^{44,45} Cyclic voltammetry has been used to measure oxidation potentials and it was concluded that in neutral or slightly basic media, the nitrenium ion 17 possessed a lifetime of one second.⁴⁴ A recent report has appeared on the anodic oxidation of a pyrrole derivative to form nitrenium ion 18.⁴⁶ The



detection of formal nitrenium ions in magic acid media has been the subject of several recent reports.^{47,48} The existence of the nitrenium ion derived from protonated nitroso benzenes 19 was improbable and instead the dication 20 was invoked to be the predominant species.⁴⁷

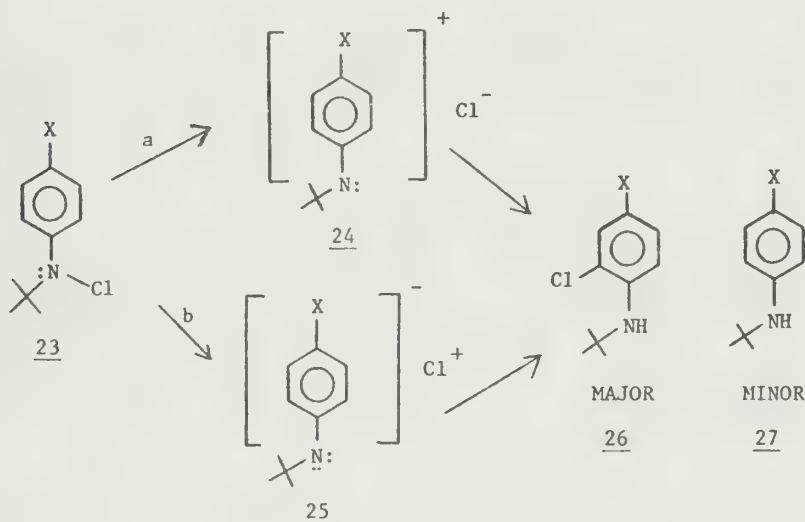


Gassman and co-workers initiated the concept of a synthetically useful nitrenium ion intermediate in the Ag^+ catalyzed methanolysis of N-chloroisoquinuclidine 21, by postulating 22 as a possible intermediate in the formation of 2-methoxy-1-azabicyclo[3.2.1]octane.^{4,9} Subsequent



product studies of other N-chloro bicyclic systems established that nucleophilic addition of solvent occurs at the carbocation center that forms by the migration of an alkyl group to an electron deficient nitrogen. In a series of kinetic studies, Gassman^{4,2b,c} has established a nitrenium ion intermediate in the thermal rearrangement of N-chloroanilines 23 to afford aniline derivatives 26 and 27 as shown in Scheme I.

Scheme I

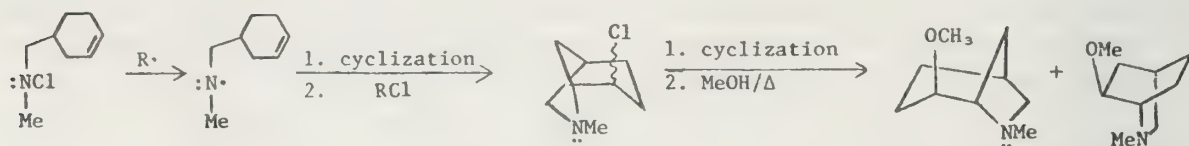


Evidence for pathway a in Scheme I was shown by a 10^6 rate increase for this rearrangement upon going from electron withdrawing substituents to electron releasing substituents. This is taken to suggest an ionic transition state with substantial charge delocalization in the aromatic ring. It was observed that in a $\sigma^+ \rho$ plot, a ρ value of -6.35 was obtained. The unusually high magnitude of ρ is not surprising due to the substantial charge delocalization into the aromatic ring, reflecting the inferior ability of nitrogen to bear a positive charge relative to carbon. It was further observed that as X became more electron withdrawing a higher yield of aniline derivative 27 occurred. To account for this a nitrenium ion singlet \rightarrow triplet spin inversion was postulated, with subsequent hydrogen abstraction by the resultant diradical cation. Thus, with the greater

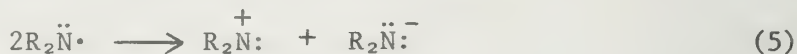
development of positive charge on nitrogen, a more facile spin inversion to the theoretically⁵¹ more stable diradical cation was invoked to explain the higher yields of the aniline derivative 27. The existence of this spin inversion was supported by a previous⁵² heavy atom solvent experiment.⁵³

Further support for the existence of discrete nitrenium ions as reactive intermediates has recently appeared. Gassman has shown through a product study that photochemically induced homolytic N-Cl bond cleavage gives rise to substantially different products than those produced in the thermal heterolytic case.⁵⁴ This study was taken to suggest that a free radical mechanism was not operative in the thermal reactions studied by Gassman.

The existence of aliphatic nitrenium ions has not been universally accepted. An alternative mode of homolytic N-Cl bond cleavage followed by subsequent neutral amine radical reactions has been invoked by Edwards to account for proposed nitrenium ion chemistry.⁴³ Principally, it was observed that the presence of radical initiators in the cyclization reaction of olefinic N-chloramines led to reaction acceleration while molecular oxygen retarded the rate substantially.^{43a} A radical chain process was suggested to account for the observed products.



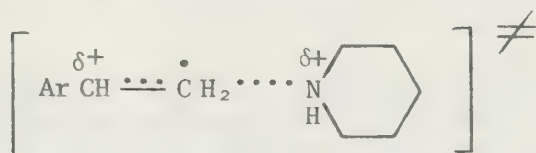
A final mechanistic pathway on the formation of aryl nitrenium ions has been considered. Evidence for the existence of an electron transfer reaction (5) of aryl amines has been presented, principally by a product study analysis.⁵⁵



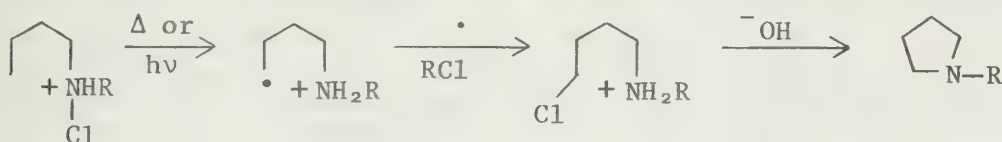
Cationic Nitrogen Radicals, 3. The generation of the electrophilic intermediate aminium radicals 3 and their addition to unsaturated systems has been of synthetic interest in the literature.^{56,57} Aminium radicals can be generated through oxidation of NH_2X molecules by transition metal cations,⁵⁷ by photochemical decomposition in acidic media of N-nitrosamines,⁵⁸ N-halamines⁵⁹ and 2-tetrazenes⁵⁶ and by thermal decomposition in acidic media of dialkyl chloramines.⁶⁰

The cationic nature of aminium radicals suggests electrophilic properties; however, the radical nature usually dictates a reactivity mode compatible with a homolytic transition state. Mechanistic evidence has been presented for an electrophilic interaction between substituted styrenes and piperidinium radicals in the form of a ρ value of -1.34 in a $\rho\sigma$ plot.⁶¹ This value is quite large for radical additions⁵⁶ and lies favorably in the direction of the ρ value -3.42 for the protonation of substituted styrenes.⁶² A transition state involving charge dispersion is suggested⁶¹ which accommodates the magnitude of ρ while development of positive charge at the benzylic position is consistent with the marked rate increase by para electron releasing groups. Further support for the electrophilic behavior of these cationic radicals is seen in the reaction of unsaturated hydrocarbons with aminium radicals and with neutral amino radicals. The former display a strong preference for addition to the

unsaturated center,⁶³ while the latter generally react in the mode of H-abstraction.⁶⁴



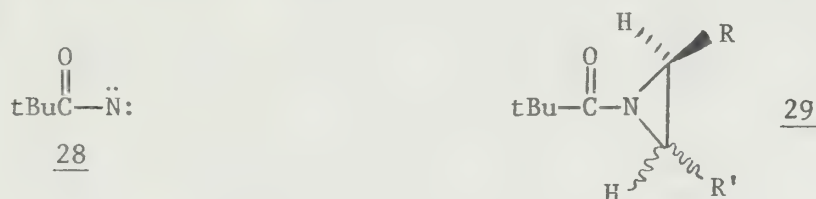
The synthetic applications of aminium radicals has been directed primarily toward the synthesis of β -substituted amines from olefins,⁵⁹ pyrrolidine derivatives from N-chloroalkylamines,⁶⁵ and aromatic amination.⁵⁷ The well known intramolecular hydrogen abstraction reaction of aminium radicals (Hofmann-Löffler-Freytag reaction)⁶⁵ is highly regio-selective with preferential hydrogen abstraction from the δ -carbon:



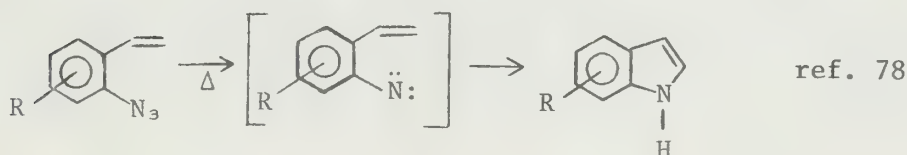
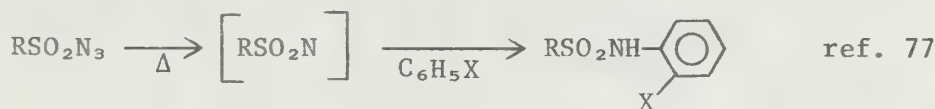
Thus, aminium radicals provide a convenient entry into a wide variety of aminated products by relatively simple routes in respectable yields.

Nitrenes, 4. The utility of nitrenes as useful electrophilic intermediates in organic synthesis has been the subject of several reviews.^{72a,b} The reactions of this electron deficient species has been restricted to C-H insertion,⁷³ N-H insertion,⁷⁴ addition to aromatic rings⁷² and addition to olefins.⁷⁵

The generation of nitrenes is usually accomplished by the thermal or photochemical decomposition of azides, deoxygenation of nitro and nitroso-compounds or oxidation of amines.^{74a} Nitrenes are capable of existing in either singlet or triplet electronic states with the latter generally being the lower energy state.⁷⁶ The different modes of reactivity for singlet and triplet nitrenes was demonstrated by the stereospecific addition of singlet pivaloyl nitrene 28 to various olefins to produce aziridine derivatives 29, whereas the triplet biradical nitrene was observed to add in a stereoselective fashion to produce 29.

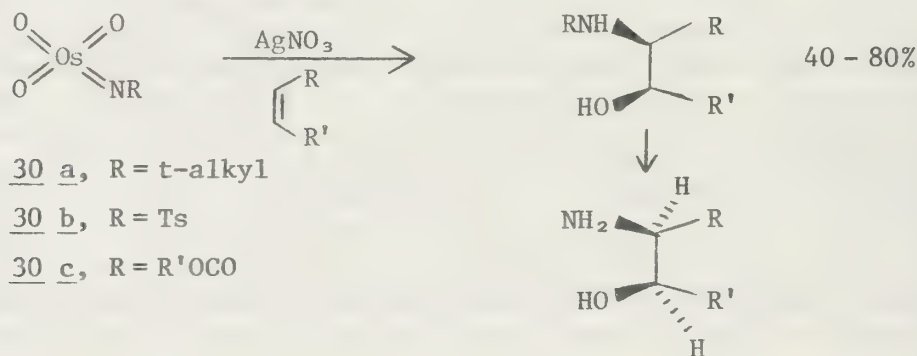


Representative reactions involving nitrene intermediates are shown below:



The involvement of nitrene intermediates has been invoked in the reaction of chloramine-T with a variety of nucleophiles.⁷⁹

Organometallic Reagents, 5. The recent reports by Sharpless of the vicinal oxyamination reaction of olefins by organo osmium reagents provides a convenient new entry into α -amino alcohols.⁸⁰ Organometallic reagents 30 a-c have been observed to add to olefins with a high degree of regioselectivity and in a cis manner. The good to excellent yields obtained as well as the simple synthetic procedures employed make this an attractive route to an important class of synthetic intermediates.



In summary, recent work has provided a number of synthetically useful electrophilic amination species. The use of heteroatom substituted amines as direct electrophilic aminating reagents suggests this approach as a possible alternative to the currently more popular nucleophilic amination reactions. Electron deficient nitrenium ions, nitrenes and aminium radicals have received a relatively modest amount of attention as useful synthetic intermediates in amination reactions, an observation that reflects the novelty and elusive character of these species. Finally, with the advent of organometallic oxyamination reagents, a new and convenient approach to functionalized amines is at hand.

BIBLIOGRAPHY

1. F. Zymalkowski, "Methodicum Chemicum", Vol. 6, Academic Press, New York, Chapter 12.
2. (a) P. Kovacic, M. K. Lowery, and K. W. Field, Chem. Rev., 639 (1970); (b) W. Theilacker and E. Wegner, Angew. Chem., 72, 127 (1960).
3. F. Raschig, Ber., 40, 4580 (1907).
4. (a) G. Yagil and M. Anbar, J. Am. Chem. Soc., 84, 1797 (1962); (b) R. A. Rowe and L. F. Audrieth, *ibid.*, 78, 563 (1956).
5. L. F. Audrieth, V. Scheibler, and M. Zimmer, J. Am. Chem. Soc., 78, 1852 (1956).
6. K. Hoegerle and H. Erlenmeyer, Helv. Chim. Acta, 39, 1203 (1956).
7. H. H. Sister *et al.*, J. Am. Chem. Soc., 81, 2982 (1959).
8. R. Appel and W. Büchner, Chem. Ber., 95, 849 (1962).
9. W. Theilacker and E. Wegner, Ang. Chem., 72, 127 (1960).
10. G. H. Coleman and C. R. Hauser, J. Am. Chem. Soc., 50, 1193 (1928).
11. G. H. Coleman and R. F. Blomquist, J. Am. Chem. Soc., 63, 1692 (1941).
12. M. Horiike, J. Oda, Y. Inover, and M. Ohno, Agric. Biol. Chem., 33, 292 (1969).
13. J. Meinwald, P. G. Gassman, and E. C. Miller, J. Am. Chem. Soc., 81, 955 (1959).

14. G. H. Coleman and R. A. Forrester, J. Am. Chem. Soc., 58, 27 (1936).
15. F. Kuffner and W. Siefried, Monatsh Chem., 83, 748 (1952).
16. (a) H. C. Brown, et al., J. Am. Chem. Soc., 86, 3565 (1964); (b) L. Verbit and P. Heffron, J. Org. Chem., 32, 3199 (1967); (c) Y. Tamura et al., Synthesis, 196 (1974); (d) H. C. Brown and G. Zweifel, J. Am. Chem. Soc., 83, 2544 (1961).
17. (a) K. Seppelt and W. Sundermeyer, Z. Naturforsch. B, 24, 774 (1969); (b) G. H. Coleman and H. L. Johnson, Inorg. Syn., 1, 59 (1939).
18. Y. Tamura, J. Minamikawa, and M. Ikeda, Synthesis, 1 (1977).
19. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, 1967, p. 481.
20. Y. Tamura et al., J. Org. Chem., 38, 1239 (1973).
21. L. A. Carpino, J. Am. Chem. Soc., 82, 3133 (1960).
22. W. N. Marmer and G. Mderker, J. Org. Chem., 37, 3520 (1972).
23. T. Sheradsky, G. Salemnick, and Z. Nir, Tetrahedron, 28, 3833 (1972).
24. E. Schmitz, Ang. Chem. Int. Ed. Eng., 3, 333 (1964).
25. E. Schmitz, Russ. Chem. Rev., 45, 1 (1976).
26. S. Oae and F. Yamamoto, Tetrahedron Lett., 5143 (1973).
27. T. Sheradsky, J. Heterocycl. Chem., 4, 413 (1967).
28. Y. Tamura et al., Tetrahedron Lett., 4137 (1972).
29. Y. Tamura et al., Tetrahedron, 29, 1063 (1973).
30. Y. Tamura et al., Tetrahedron Lett., 4133 (1972).
31. W. M. Marmer and G. Maerker, J. Org. Chem., 37, 3520 (1972).
32. L. A. Capino, J. Org. Chem., 30, 321 (1965).
33. The diamine salt can be obtained in 65% yield from nicotine. See ref. 29.
34. C. R. Johnson, R. A. Kirchhoff, and H. G. Corkins, J. Org. Chem., 39, 2458 (1974).
35. Y. Tamura et al., Synthesis, 312 (1973).
36. Y. Tamura et al., Tetrahedron, 31, 3035 (1975).
37. S. Yamada et al., J. Chem. Soc. Chem. Commun., 623 (1972).
38. T. Sheradsky and Z. Nir, Tetrahedron Lett., 77 (1969).
39. D. I. Scopes, A. F. Kluge, and J. A. Edwayds, J. Org. Chem., 42, 376 (1977).
40. G. Zinner and E.-U. Ketz, Synthesis, 165 (1973).
41. E. Schmitz, Zhur. Geterotsikl. Sved., 1629 (1974).
42. (a) P. G. Gassman, Acct. Chem. Res., 3, 26 (1970); (b) P. G. Gassman, G. A. Campbell, and R. C. Frederick, J. Am. Chem. Soc., 94, 3884 (1972); (c) P. G. Gassman and G. A. Campbell, ibid., 94, 3891 (1972); (d) P. G. Gassman and G. Hartman, ibid., 95, 449 (1973).
43. (a) O. E. Edwards et al., Can. J. Chem., 52, 2123 (1974); (b) O. E. Edwards, D. Vocelle, and J. W. ApSimon, Can. J. Chem., 50, 1167 (1972).
44. D. Serve, J. Am. Chem. Soc., 97, 432 (1975).
45. V. Svanholm and V. D. Parker, J. Am. Chem. Soc., 96, 1234 (1974).
46. D. Serve et al., J. Electroanal. Chem., 87, 353 (1978).
47. G. A. Olah and D. J. Donovan, J. Org. Chem., 43, 1743 (1978).
48. T. Okamoto et al., Tetrahedron Lett., 101, 105 (1977).
49. (a) P. G. Gassman and B. L. Fox, Chem. Commun., 153 (1966); (b) P. G. Gassman and B. L. Fox, J. Am. Chem. Soc., 89, 338 (1967).
50. (a) P. G. Gassman and R. L. Cryberg, J. Am. Chem. Soc., 90, 1355 (1968); (b) P. G. Gassman and R. L. Cryberg, ibid., 91, 2047 (1969).
51. Ab initio SCF-CI calculations for the triplet — singlet spin inversion indicates that the triplet state lies 45 kcal/mole lower in energy than the singlet. See: S. J. Lee and K. Morokuma, J. Am. Chem. Soc., 93, 6863 (1971).
52. P. G. Gassman and R. L. Cryberg, J. Am. Chem. Soc., 91, 5176 (1969).

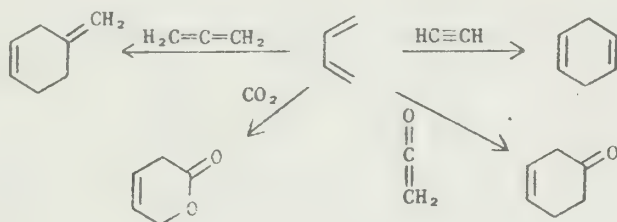
53. The coupling of spin and angular moments of solvent heavy atoms (Br) with radicals in a spin inversion process is well known. See: A. G. Anastassiou, J. Am. Chem. Soc., 88, 2322 (1966).
54. P. G. Gassman, K. Uneyama, and J. L. Hahnfeld, J. Am. Chem. Soc., 99, 647 (1977).
55. J. I. G. Cadogan and A. G. Rowley, J. Chem. Soc. Perkin II, 1030 (1974).
56. Y. L. Chow et al., Chem. Rev., 78, 243 (1978) and references cited therein.
57. F. Minisci, Synthesis, 1 (1973).
58. Y. L. Chow, Accts. Chem. Res., 6, 354 (1973).
59. R. S. Neale, Synthesis, 1 (1971).
60. E. J. Corey and W. R. Herther, J. Am. Chem. Soc., 82, 1657 (1966).
61. T. Mojelsky and Y. L. Chow, J. Am. Chem. Soc., 96, 4549 (1974).
62. W. M. Schubert, B. Lam, and J. R. Reece, J. Am. Chem. Soc., 86, 4727 (1966).
63. (a) R. S. Neale, J. Org. Chem., 32, 3273, 3263 (1967); (b) R. S. Neale and N. L. Marcus, ibid., 32, 3457 (1968); (c) H. Bock and K. Kompa, Chem. Ber., 99, 1347, 1357, 1361 (1966); (d) F. Minisci and R. Galli, Tetrahedron Lett., 2531 (1966).
64. (a) B. R. Cowley and W. A. Waters, J. Chem. Soc., 1228 (1961); (b) D. Mackay and W. A. Waters, J. Chem. Soc. (C), 813 (1966); (c) R. E. Jacobson, K. M. Johnston, and G. H. Williams, Chem. and Ind., 157 (1967).
65. M. E. Wolff, Chem. Rev., 63, 55 (1963).
66. C. J. Albisetti et al., J. Am. Chem. Soc., 81, 1489 (1952).
67. Y. L. Chow et al., J. Org. Chem., 32, 2109 (1967).
68. F. Minisci, R. Galli, and M. A. Rossetti, Chim. Ind. (Milan), 49, 447 (1972).
69. F. Furstoss et al., Tetrahedron Lett., 1263 (1970).
70. F. Minisci and V. Malatesta, Chim. Ind. (Milan), 53, 1154 (1971).
71. F. Minisci, R. Galli, and M. Cecere, Tetrahedron Lett., 4663 (1965).
72. (a) R. K. Smalley and H. Suschitzky, Chem. and Ind., 100, 1338 (1970); (b) R. A. Abramovitch and B. A. Davis, Chem. Rev., 64, 149 (1964).
73. M. F. Sloan, D. S. Breslow, and W. B. Renfrow, Tetrahedron Lett., 2905 (1964).
74. (a) E. F. V. Scriven and H. Suschitzky, Tetrahedron Lett., 103 (1973); (b) R. E. Banks and A. Prakash, ibid., 99 (1973); (c) P. A. S. Smith and H. Dounchis, J. Org. Chem., 38, 2958 (1973).
75. (a) G. R. Felt and W. Lwonski, J. Org. Chem., 41, 96 (1976); (b) Y. Hayashi and D. Swern, J. Am. Chem. Soc., 95, 5205 (1973).
76. J. T. Sharp, Ann. Rep. Chem. Soc. B, 70, 184 (1973).
77. R. A. Abramovitch et al., J. Org. Chem., 39, 1101 (1974).
78. R. J. Sundberg et al., J. Heterocycl. Chem., 6, 441 (1969).
79. L. Horner and A. Christmann, Ang. Chem. Int. Ed. Eng., 2, 599 (1963).
80. (a) K. B. Sharpless, A. Chong, and K. Oshima, J. Org. Chem., 41, 177 (1976); (b) K. B. Sharpless, S. Biller, and E. Herrnaz, J. Am. Chem. Soc., 100, 3596 (1978); (c) K. B. Sharpless, A. O. Chong, and K. Oshima, ibid., 99, 3420 (1977); (d) K. B. Sharpless et al., J. Org. Chem., 43, 2628 (1978).

DIENOPHILE SYNTHETIC EQUIVALENTS IN THE DIELS-ALDER REACTION

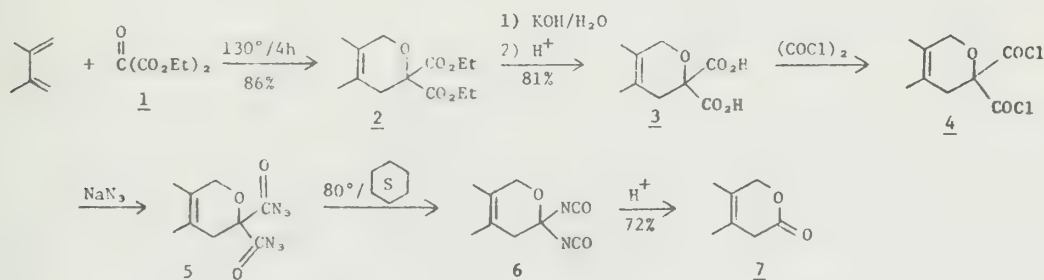
Reported by Stephen D. Harper

September 14, 1978

Attractive routes for the synthesis of complex organic compounds often can be envisioned by $\pi_S^4 + \pi_S^2$ (Diels-Alder) cycloaddition of a 1,3 diene to allene, ketene, acetylene, or carbon dioxide. However, these simple units react sluggishly, if at all, as dienophiles. Consequently, the development of useful synthetic equivalents of these π_S^2 systems is of great interest. The functional groups in the synthetic equivalents which provide facile cycloaddition must subsequently be readily transformed under mild conditions to carbon-oxygen or carbon-carbon double bonds or to a carbon-hydrogen bond.



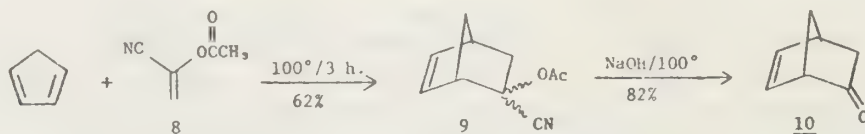
Carbon Dioxide Equivalents. Carbon dioxide is inert towards 1,3 dienes in thermal cycloadditions.¹ Development of a π_S^2 synthetic equivalent would therefore appear to be highly desirable. However, only one method which provides that species has been developed to date. Diethyl ketomalonate (1) has been found to add to several simple dienes to produce diesters such as 2.² The diester is hydrolyzed to obtain the corresponding diacid 3, which is converted to bisacylazide 5 using sodium azide. Curtius rearrangement of the bisacylazide provides the bisisocyanate 6. Mild hydrolysis then leads to the desired lactone 7 in good overall yield. If the lactone produced is not stable to the hydrolytic conditions of the last step, ring opened dienoic acids are produced. The 1,3 dienes employed must be of intermediate Diels-Alder reactivity, as anthracene and cyclopentadiene adducts are not isolated.



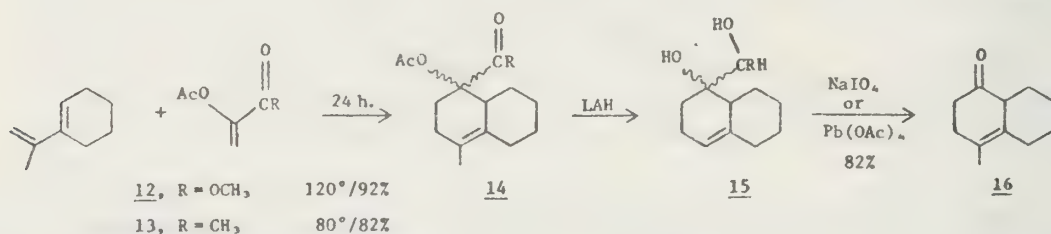
Ketene Equivalents. Ketenes generally undergo 1,2 cycloaddition when heated with alkyl substituted 1,3 dienes.³ Thus, a ketene equivalent⁴ which is useful in a $\pi_S^4 + \pi_S^2$ cycloaddition provides a formal reaction pathway which is not followed by a parent system.

Bartlett found that α -acetoxycrylonitrile (8) adds to cyclopentadiene.⁵ The resulting adduct 9 is hydrolyzed to yield norbornenone 10. Although other workers have used this reagent as a ketene equivalent in reactions with dihydroanisole derivatives,⁶ dimethyl fulvene,⁷ and

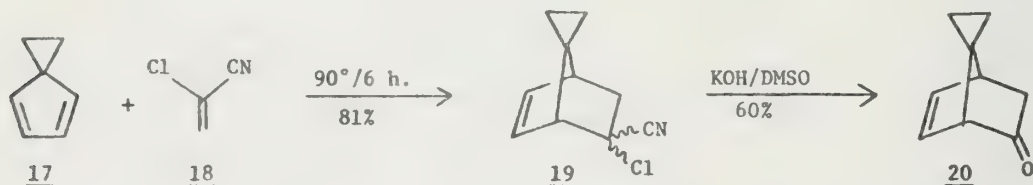
1-isopropenyl cyclohexene,⁸ good yields result only under relatively harsh conditions. High temperatures are required for the cycloaddition and conversion of the adduct to the ketone uses strong base.



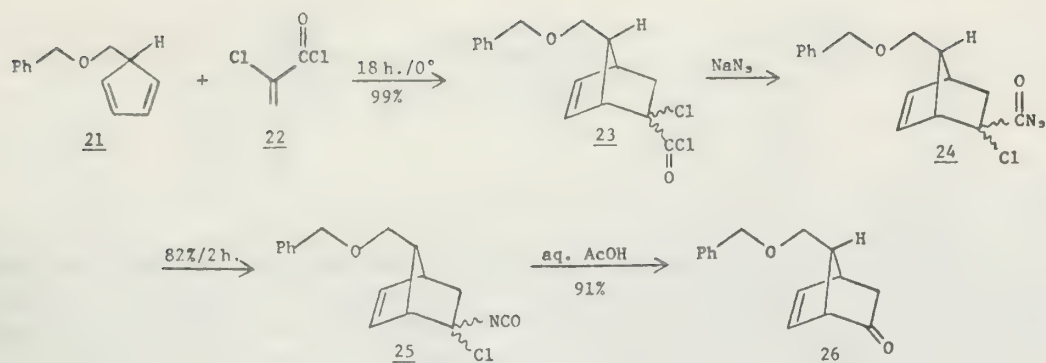
Wharton and Aw observed that higher yields of ketone 6 are obtained when methyl α -acetoxyacrylate (12) or α -acetoxyvinyl methyl ketone (13) is used as a dienophile in reactions with 1-isopropenyl cyclohexene (11). Reduction of adduct 14 with lithium aluminum hydride and oxidative cleavage of the resulting diol 15 leads to the desired product.



2-Chloroacrylonitrile (18), which is both more reactive and regio-selective than α -acetoxyacrylonitrile,⁶ has been successfully used as a ketene equivalent by numerous workers.^{6,9} Fulvene, cyclopentadiene, and dihydroanisoole derivatives have usually served as the diene component in the cycloaddition step. For example, cyclopentadiene 17 adds in good yield to 18 in refluxing benzene. The resulting adduct 19 is converted to the desired norbornenone 20 by treatment with base. An interesting modification of this procedure uses the readily available acrylonitrile as the dienophile, followed by chlorination of the adduct with phosphorous pentachloride and base hydrolysis.^{9d,10}

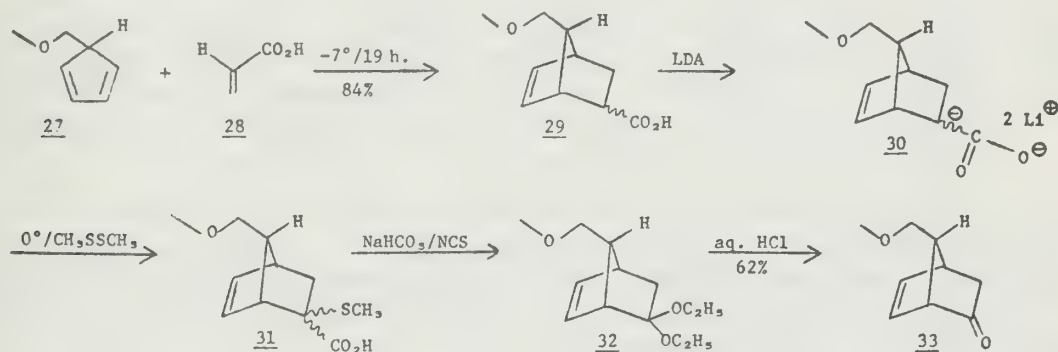


An alternative ketene equivalent was developed by Corey¹¹ for use in the synthesis of 7-syn-substituted norbornenones. An especially reactive species is required because the 5-substituted cyclopentadienes used as the 1,3 diene component readily isomerize when heated or in the presence of acid or base. The use of 2-chloroacryloyl chloride (22) permits cycloaddition to proceed at low temperature without isomerization. Adduct 23 is isolated in nearly quantitative yield, for example. Reaction with sodium azide, followed by Curtius rearrangement and hydrolysis, leads in high yields to the desired norbornenone 26. Dienes such as anthracene and substituted butadienes also react readily with 2-chloroacryloyl chloride. Two disadvantages of the method are the formation of potentially hazardous azides and the difficult preparation of the 2-chloroacryloyl chloride reagent.

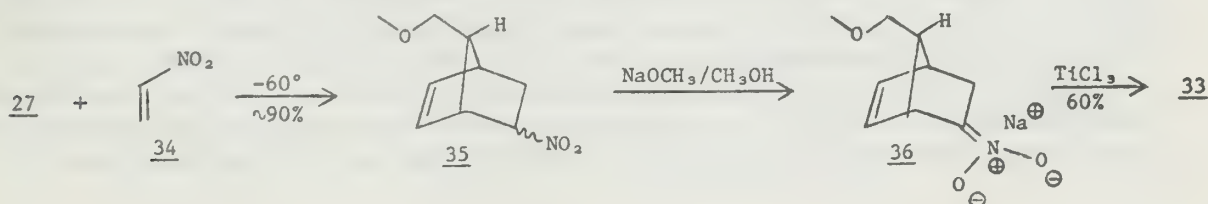


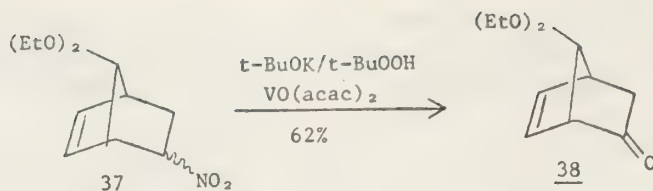
Two reactive mono-substituted ethylenes which have recently been exploited as ketene equivalents are acrylic acid and nitroethylene. The synthetic usefulness of these compounds has not yet been fully determined as only 1,3 cyclohexadiene, cyclopentadiene, and 5-substituted cyclopentadienes have been employed as dienes in the cycloaddition.

5-Methyl methoxy cyclopentadiene (**27**), for example, undergoes smooth cycloaddition at low temperature to acrylic acid (**28**).¹² Sulfenylation of the dianion **30** generated by means of lithium diisopropylamide yields **31**. Addition of N-chlorosuccinimide in the presence of mild base provides ketal **32**, which may be transformed by hydrolysis to the desired 7-syn-substituted norbornenone **33** in good overall yield.



Like acrylic acid, nitroethylene is a potent dienophile. High yields of adduct **35** result from the reaction of nitroethylene (**34**) with cyclopentadiene **27** at -60° , for example.¹³ Two methods to effect the conversion of the nitro group in the Diels-Alder adduct to a carbonyl function under relatively mild conditions have been developed. The conversion of **35** to **33** is achieved in good yield by treatment of **35** with sodium methoxide followed by addition of buffered TiCl_3 .¹⁴ Alternatively, reaction of t-butyl peroxide, t-butoxide, and vanadyl acetyl acetonate with adduct **37** affords comparable yields of ketone **38**.¹³

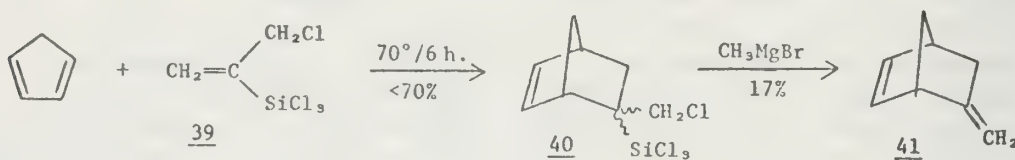




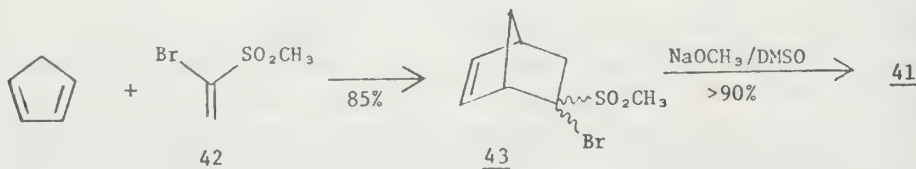
In summary, 2-chloroacryloyl chloride appears to be the best available ketene equivalent if high yields and mild reaction conditions are of primary concern. Nitroethylene and acrylic acid are attractive alternatives which deserve further investigation with a greater variety of 1,3 dienes.

Allene Equivalents. Although allenes containing electron withdrawing groups are often good dienophiles,¹⁵ allene itself reacts only at elevated temperatures even with normally reactive 1,3 dienes.^{15b}

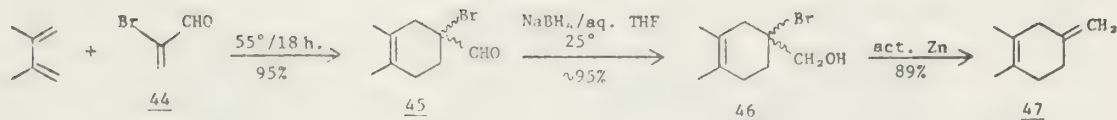
The first allene synthetic equivalent reported was 3-chloro-2-trichlorosilyl propene (39).¹⁶ This compound is prepared in low yield from propargyl chloride and trichlorosilane. 1,3 Butadiene and cyclopentadiene have been the only dienes used in the cycloaddition step. The latter adds to 39 to produce adduct 40, which upon treatment with methyl magnesium bromide undergoes elimination to give 5-methylene-2-norborenone (41) in poor yield.



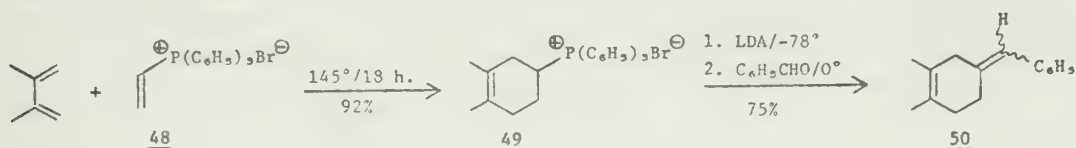
Better yields of 41 are obtained using methyl α -bromovinyl sulfone (42).¹⁷ Addition to cyclopentadiene occurs in good yield and the resulting mixture of α -bromo sulfone isomers 43 is readily transformed via Ramberg-Backlund rearrangement to 41. Cyclopentadiene has been the only diene used in the cycloaddition step.



Snider successfully employed α -bromoacrolein (44) as an allene equivalent in cycloadditions to 2,3-dimethylbutadiene, cyclopentadiene, trans, trans-1,4-diphenylbutadiene, and anthracene.¹⁸ Diels-Alder adduct 45, for example, is produced in high yield from the reaction of α -bromoacrolein with 2,3-dimethylbutadiene. Reduction of 45 with sodium borohydride affords excellent yields of the corresponding bromohydrin 46. Dehalohydrination occurs upon reaction with activated zinc to produce the desired cyclohexene 47. The regioselectivity of the cycloaddition step is not known as only symmetrically substituted dienes have been used.



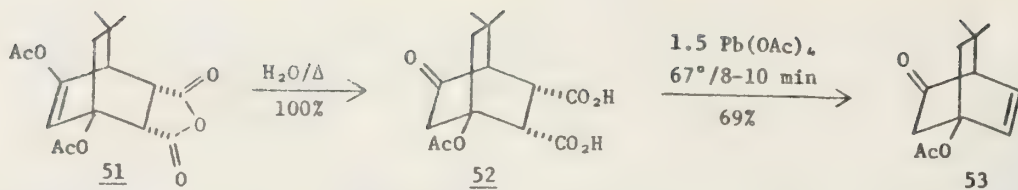
Vinyltriphenylphosphonium bromide (48) acts as a dienophile, undergoing 1,4 cycloaddition at elevated temperature to cyclopentadiene, 1,3-cyclohexadiene, or methyl substituted 1,3-butadienes.^{2b,19} For example, excellent yields of adduct 49 are obtained upon reaction of 48 with 2,3-dimethylbutadiene. Conversion of 49 to the corresponding ylide is followed by Wittig condensation with benzaldehyde to yield 50 as a mixture of Z and E isomers. A variety of aldehydes including formaldehyde have been used in the condensation step, although yields are quite variable. Tetra-substituted olefins cannot be prepared using this procedure. However, the regioselectivity observed with unsymmetrically substituted 1,3 dienes in the cycloaddition step appears to be high.



α -Bromoacrolein appears to be the best allene synthetic equivalent developed to date. It is a much more reactive dienophile than vinyltriphenylphosphonium bromide and its adducts may be converted to the desired olefinic products in consistently high yields. Although not all functional groups which may be present on the 1,3 diene component will survive treatment with sodium borohydride and activated zinc, the other methods available employ reagents such as strong base which may be equally destructive.

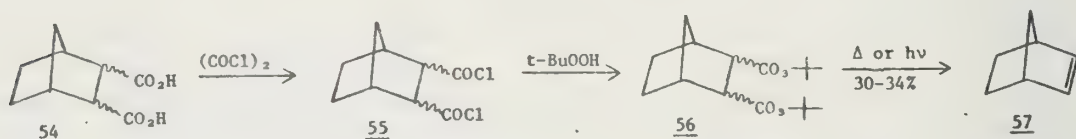
Acetylene Equivalents. While addition of acetylene as a dienophile to 1,3 dienes can be forced,²⁰ the high temperature and pressure necessary to effect the reaction have encouraged the development of acetylene synthetic equivalents. Three general approaches have been devised to date. The first employs a reactive dienophile to facilitate the Diels-Alder addition. The adduct formed is generally not readily transformed to the desired olefin. The second route relies on a more sluggish dienophile whose substituents may be removed under mild conditions. In the third approach, thermal elimination of fragments from the Diels-Alder adduct occurs to yield the product, usually without isolation of the intermediate adduct.

Maleic anhydride and dimethyl acetylene dicarboxylate are both very reactive dienophiles. The problems associated with bis-decarboxylation of the resulting Diels-Alder adducts detract from the usefulness of these compounds as acetylene synthetic equivalents. Lead dioxide when heated with vicinal dicarboxylic acid gives poor yields of olefin.²¹ Use of lead tetraacetate²² results in improved yields under less harsh conditions. Yields are generally highest when short reaction times in the presence of oxygen and excess lead tetraacetate are employed.^{22d,e} For example, diacid 52, obtained in quantitative yield from maleic anhydride adduct 51, is bis-decarboxylated to produce olefin 53 in 69% yield.



Extensive lactonization can occur using lead tetraacetate, particularly in cases where the adduct contains a double bond in close proximity to the carboxylic acid functions.^{22d} This problem is alleviated in most instances by the use of electrolysis to introduce the double bond, although yields are generally only fair. The method is somewhat impractical for use on a preparative scale.

An alternative approach to bis-decarboxylation involves formation of di-*t*-butyl peresters.²⁴ For example, reaction of diacid chloride 55, derived from diacid 54, with *t*-butyl peroxide produces high yields of di-*t*-butyl perester 56. Low yields of alkene 57 are obtained by thermal or photochemical decomposition.



Copper metal²⁵ and cuprous oxide²⁷ catalyze the bisdecarboxylation of many different types of vicinal diacids in yields comparable to or higher than those obtained through previously described methods. However, the high reaction temperatures required promote retro Diels-Alder reactions and formation of undesired aromatic products.

The transition metal complex bis(triphenylphosphine) nickel dicarbonyl converts maleic anhydride adducts directly to olefins.²⁷ Although good yields can be achieved, elevated temperatures are necessary. In addition, adducts with readily abstractable β hydrogens form complex reaction mixtures.^{27a} Diiron nonacarbonyl and tris-triphenylphosphine rhodium chloride, as well as the nickel complex previously mentioned, effect the transformation of the corresponding thio-anhydrides to olefins.^{27a,28}

To avoid the difficult bis-decarboxylation step, dienophiles containing functional groups which can be more efficiently removed have been employed. Harsher reaction conditions in the cycloaddition are required with all such synthetic equivalents developed thus far, reducing the usefulness of this approach. All acetylene equivalents in this category have been used only with specific 1,3 dienes and not developed further.

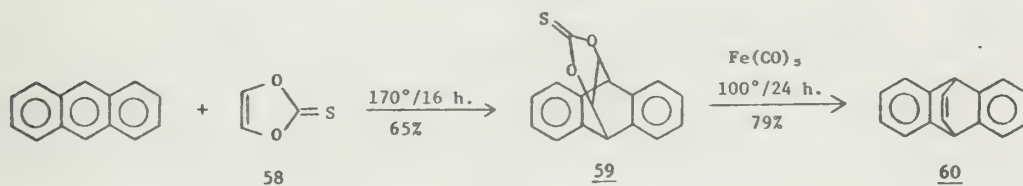
The earliest reported acetylene synthetic equivalents were vinyl halides, whose Diels-Alder adducts are readily dehydrohalogenated upon heating.²⁹ 1,2-Dichloroethylene, in either *cis* or *trans* form, is a slightly better dienophile than mono-halogenated ethylenes, although good yields in reactions with anthracene require heating at 200° for 24 hours. Dechlorination of the resulting adducts occurs in high yield

upon treatment with sodium. The dechlorination conditions are too harsh for anthracenes substituted with cyano, chlorine, or ester groups in the 2 position to be used as the diene component.²⁵

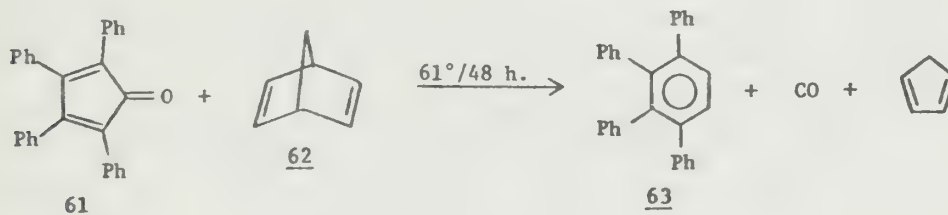
Trans- β -chloroacrylic acid adds to elevated temperatures to 1,1,4,4-d₄-butadiene.³¹ The salt of the resulting adduct is transformed readily to 3,3,6,6-d₄-butadiene using hexamethylphosphoramide and sodium iodide. Anthracene adducts of cis or trans- β -bromoacrylic acid are converted in low yield to dibenzobarrelene by base.³²

Methyl vinyl ketone and methyl acrylate have been employed as acetylene equivalents in the synthesis of barrelene from α -pyrone.³³ Conversion of the desired adducts, separated in low yield from complex mixtures of isomers, to barrelene requires several steps.

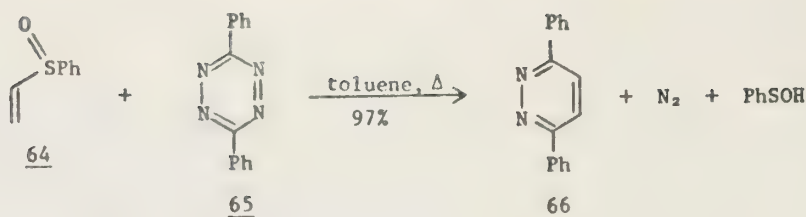
2-Thio-1,3-dioxol-4-ene (58) and 2-phenyl-1,3-dioxol-4-ene, obtained via multi-step syntheses from furan and vinylene carbonate,³⁴ add in moderate yield to anthracene at 170°. ³⁵ Thiocarbonate adducts such as 59 are converted to the desired olefins by a number of reagents, including trialkyl phosphites,³⁶ iron pentacarbonyl,³⁵ and bis (1,5-cyclooctadiene) nickel (0).³⁷ The last reagent effects the transformation under particularly mild conditions. Conversion of 2-phenyl-1,3-dioxolane adducts to olefins is achieved by means of *n*-butyl lithium.³⁸



Dienophiles which add to 1,3 dienes and subsequently undergo thermal degradation to olefin constitute a third class of acetylene synthetic equivalents. Tetrasubstituted cyclopentadienes, for example 61, react readily with norbornadienes such as 62.³⁹ Upon further heating, carbon monoxide and cyclopentadienes are eliminated. The synthetic utility of the method is limited, as the desired product must be unreactive towards the cyclopentadienes evolved.



Phenyl vinyl sulfoxide (64) also serves as an acetylene synthetic equivalent.⁴⁰ For example, diphenyl-*s*-tetrazine (65) produces excellent yields of 1,4-diphenylpyridazine (66) when heated with 64 in toluene. Mixtures of products result in cases where elimination of phenyl sulfenic acid can occur in more than one direction. The phenyl sulfenic acid produced may react with the cyclo-adduct from which it was eliminated.



In summary, all reaction schemes involving acetylene synthetic equivalents which have been developed to date have serious shortcomings. The use of high temperatures at one or more steps in the reaction sequence or severe restrictions on the type of compound that can be synthesized are the two most common faults.

BIBLIOGRAPHY

1. J. Hamer and J. A. Turner, "1,4-Cycloadditions", J. Hamer, Ed., Academic Press, New York, N.Y., 1967, pp. 205-215, and references cited therein.
2. (a) R. A. Ruden and R. Bonjouklian, J. Am. Chem. Soc., 97, 6892 (1975); (b) R. Bonjouklian and R. A. Ruden, J. Org. Chem., 42, 4095 (1977).
3. J. C. Martin, P. G. Gott, V. W. Goodlett, and R. H. Hasek, J. Org. Chem., 30, 4175 (1965).
4. For a review of ketene equivalents see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, Synthesis, 5, 289 (1977).
5. P. D. Bartlett and B. E. Tate, J. Am. Chem. Soc., 78, 2473 (1956).
6. D. A. Evans, W. L. Scott, and L. K. Truesdale, Tetrahedron Lett., 121 (1972).
7. C. H. DePuy and P. R. Story, J. Am. Chem. Soc., 82, 627 (1960).
8. P. S. Wharton and B. T. Aw, J. Org. Chem., 31, 3787 (1966).
9. (a) J. Paasivirta and H. Krieger, Suom. Kemistil. B, 38, 182 (1965); (b) H. Krieger and S.-E. Masar, Suom. Kemistil. A, 39, 119 (1966); (c) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Am. Chem. Soc., 91, 5675 (1969); (d) H. Krieger and F. Nakajima, Suom. Kemistil. B, 42, 314 (1969); (e) H. Krieger and S.-E. Masar, *ibid.*, 43, 318 (1970); (f) E. J. Corey, U. Koelliker, and J. Neuffer, J. Am. Chem. Soc., 93, 1489 (1971); (g) J. Ipaktschi, Chem. Ber., 105, 1840 (1972); (h) E. D. Brown, R. Clarkson, T. J. Leeney, and G. E. Robinson, J. Chem. Soc. Chem. Commun., 642 (1974); (i) E. D. Brown and T. J. Leeney, *ibid.*, 39 (1975); (j) H. L. Goering and C.-S. Chang, J. Org. Chem., 40, 2565 (1975).
10. P. K. Freeman, D. M. Balls, and D. J. Brown, *ibid.*, 33, 2211 (1968).
11. E. J. Corey, T. Ravindranathan, and S. Terashima, J. Am. Chem. Soc., 93, 4326 (1971).
12. (a) B. M. Trost and Y. Tamaru, *ibid.*, 97, 3528 (1975); (b) B. M. Trost and Y. Tamaru, *ibid.*, 99, 3101 (1977).
13. P. A. Bartlett, F. R. Green III, and T. R. Webb, Tetrahedron Lett., 331 (1977).
14. (a) S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, J. Am. Chem. Soc., 96, 5261 (1974); (b) J. E. McMurry and J. Melton, J. Org. Chem., 38, 4367 (1973).
15. (a) D. R. Taylor, Chem. Rev., 67, 317 (1967) and references cited therein; (b) T. F. Rutledge, "Acetylenes and Alkenes", Reinhold, New York, N.Y., 1969, pp. 78-80 and references cited therein.
16. R. F. Cunico and E. M. Dexheimer, Organomet. Chem. Synth., 1, 253 (1971).

17. J. C. Philips and M. Oku, J. Am. Chem. Soc., 94, 1012 (1972).
18. B. B. Snider, J. Org. Chem., 38, 3961 (1973).
19. R. A. Ruden and R. Bonjouklian, Tetrahedron Lett., 2095 (1974).
20. Rutledge, pp. 189 and references cited therein.
21. (a) W. von E. Doering, M. Farber, and A. Sayigh, J. Am. Chem. Soc., 74, 4370 (1952); (b) W. von E. Doering and M. Finkelstein, J. Org. Chem., 23, 141 (1958).
22. (a) C. A. Grob, M. Ohta, and A. Weiss, Angew. Chem., 70, 343 (1958); (b) E. E. van Tamelen and S. P. Pappas, J. Am. Chem. Soc., 85, 3297 (1963); (c) S. Masamune, H. Cuts, and M. G. Hogben, Tetrahedron Lett., 1017 (1966); (d) C. M. Cimarusti and J. Wolinsky, J. Am. Chem. Soc., 90, 113 (1968); (e) C. W. Jefford, T. W. Wallace, and M. Acar, J. Org. Chem., 42, 1654 (1977).
23. (a) P. Radlick, R. Klem, S. Spurlock, J. J. Sims, E. E. van Tamelen, and T. Whitesides, Tetrahedron Lett., 5117 (1968); (b) H. H. Westberg and H. J. Dauben, Jr., *ibid.*, 5123 (1968); (c) L. A. Paquette and M. J. Wyvratt, J. Am. Chem. Soc., 96, 4671 (1974).
24. E. N. Cain, R. Vukov, and S. Masamune, Chem. Commun., 98 (1969).
25. H. P. Figes and A. Dralants, Tetrahedron, 28, 3031 (1972).
26. R. A. Snow, C. R. Degenhardt, and L. A. Paquette, Tetrahedron Lett., 4447 (1976).
27. (a) B. M. Trost and F. Chen, *ibid.*, 2603 (1971); (b) P.-T. Ho, S. Oida, and K. Wiesner, Chem. Commun., 883 (1972); (c) P.-T. Ho, R. C. Jain, S. F. Lee, S. Oida, and A. Philipp, Can. J. Chem., 51, 1448 (1973); (d) W. G. Dauben, G. T. Rivers, R. J. Twieg, and W. T. Zimmerman, J. Org. Chem., 41, 887 (1976).
28. M. Verbeek, H.-D. Scharf, and F. Korter, Chem. Ber., 102, 2471 (1969).
29. (a) K. Alder and H. F. Rickert, Justus Liebigs Ann. Chem., 543, 1 (1939); (b) G. Komppa and S. Beckmann, *ibid.*, 512, 172 (1934).
30. (a) S. J. Cristol and N. L. Hause, J. Am. Chem. Soc., 74, 2193 (1952); (b) S. J. Cristol and R. K. Bly, *ibid.*, 82, 6155 (1960).
31. W. P. Norris, J. Org. Chem., 33, 4540 (1968).
32. (a) W. R. Vaughan and A. C. Schoenthaler, J. Am. Chem. Soc., 79, 5777 (1957); (b) W. R. Vaughan and A. C. Schoenthaler, *ibid.*, 80, 1956 (1958).
33. H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. A. Sherwin, *ibid.*, 91, 2330 (1969).
34. W. K. Anderson and R. H. Dewey, *ibid.*, 95, 7161 (1973).
35. J. Daub, U. Erhardt, J. Kappler, and V. Trautz, J. Organomet. Chem., 69, 423 (1974).
36. (a) E. J. Corey and R. A. E. Winter, J. Am. Chem. Soc., 85, 2677 (1963); (b) E. J. Corey, F. A. Corey, and R. A. E. Winter, *ibid.*, 87, 935 (1965).
37. M. F. Semmelhack and R. D. Stauffer, Tetrahedron Lett., 2667 (1973).
38. (a) J. N. Hines, M. J. Peagram, G. H. Whitman, and M. Wright, Chem. Commun., 1593 (1968); (b) G. H. Whitman and M. Wright, J. Chem. Soc. C, 883,886,891 (1971).
39. K. MacKenzie, J. Chem. Soc., 473 (1960).
40. L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, J. Am. Chem. Soc., 100, 1597 (1978).

INVESTIGATIONS OF THE SILICON-CARBON $p\pi-p\pi$ DOUBLE BOND

Reported by Reg Forbus

September 25, 1978

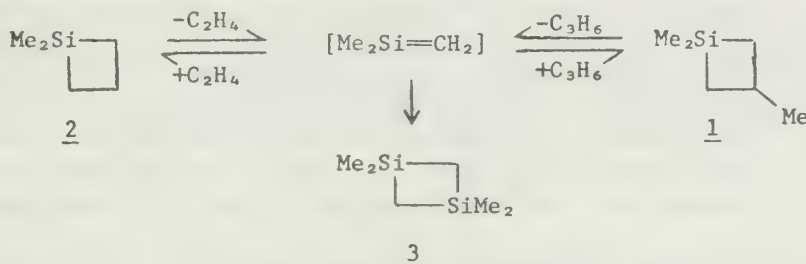
The silicon-carbon sigma bond which is described by the overlap of sp^3 hybrid orbitals is found in a wide variety of stable molecules. However, despite the great abundance of stable $p\pi-p\pi$ multiple-bonds found in compounds of carbon, stable silicon analogues with $p\pi-p\pi$ bonds to carbon are non-existent. This interesting contrast has caught the attention of a number of researchers.

Efforts to prepare molecules containing a silicon-carbon double-bond to study their characteristics have been successful only in providing transient species. Intermediates containing a silicon-carbon double bond have been generated by a variety of methods, including: cycloreversion of silacyclobutanes, thermal and photochemical rearrangements and elimination reactions. Molecular orbital calculations have aided in the understanding of the nature of these intermediates. Recent investigations of the silicon-carbon double bond are the basis of this abstract.

Cycloreversions of Silacyclobutanes. In 1966, Gusel'nikov, *et al.*, postulated the first supportive case for the intermediacy of a species having a Si-C double bond.¹ Pyrolysis of monosilacyclobutanes resulted in the clean formation of ethylene and 1,3-disilacyclobutanes. By analogy, with cyclobutane pyrolyses² which produce olefinic products, the 1,3-disilacyclobutanes were suggested to be formed via dimerization of an unstable silaethylene intermediate.

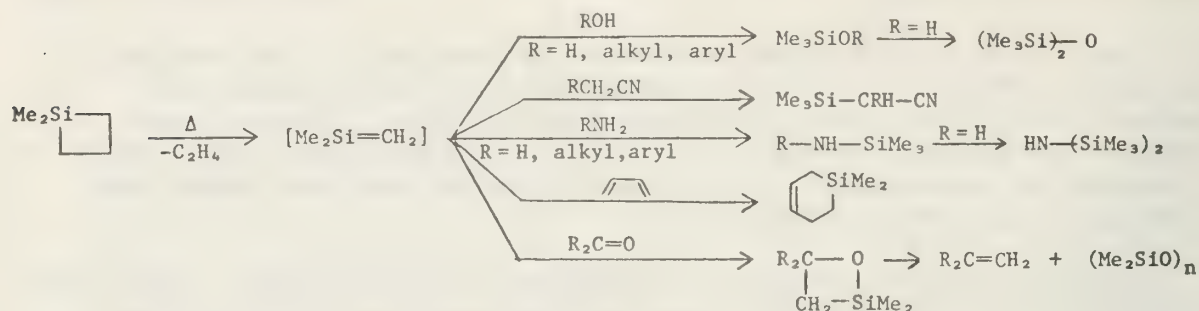
Kinetic evidence supports a similarity of mechanism. Both are first-order in substrate and the Arrhenius parameters for homogenous unimolecular thermal decomposition of 1,1-dimethylsilacyclobutane³ and 1,1-dimethylcyclobutane⁴ are in close agreement, $k(\text{sec}^{-1}) = 10^{15.6} \exp(-62300/RT)$ and $10^{15.68} \exp(-61000/RT)$, respectively.

The reversibility of the decomposition of silacyclobutanes to olefins and silaolefins was demonstrated in studies of the pyrolysis of substituted and unsubstituted 1,1-dimethylsilacyclobutanes in the presence of olefins. Copyrolysis of 1,1,3-trimethylsilacyclobutane (1) in the presence of excess ethylene and 1,1-dimethylsilacyclobutane (2) in the presence of excess propylene yields in addition to the usual products, 1,1,3,3-tetramethyl-1,3-disilacyclobutane (3), ethylene (from 2) and propylene (from 1), 2 and 1, respectively.

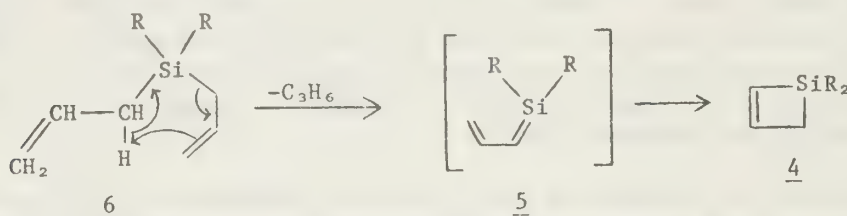


Further evidence that silaethylenes are formed upon pyrolysis of silacyclobutanes is provided by numerous trapping experiments. Copyrolysis experiments of silacyclobutanes with water,³ ammonia,³ alcohols,^{3,6} amines,⁶ ketones,^{6,7} phenols,⁶ dienes⁵ and nitriles^{6,8} give adducts from

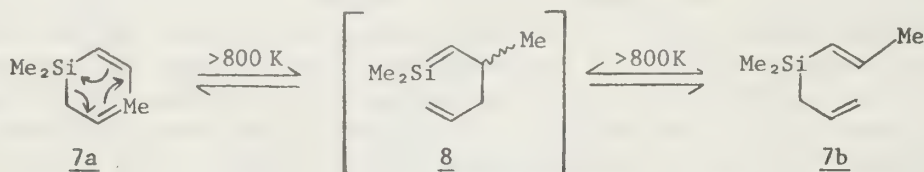
an apparent addition across the Si-C double bond. Some of these adducts are unstable and give further reacted and/or rearranged products.



Thermal Rearrangements. Silaethylenes have been generated from precursors other than silacyclobutanes by thermal rearrangements, including retro-ene reactions, [3,3] sigmatropic shifts and rearrangements in carbenes. 1,1-Dialkylsilacyclobut-2-enes (4) have been prepared by presumably a [2+2] electrocyclic reaction of 1,1-dialkylsila-1,3-butadiene (5) formed by the loss of propene in a retro-ene reaction of diallyldialkylsilanes (6).⁹



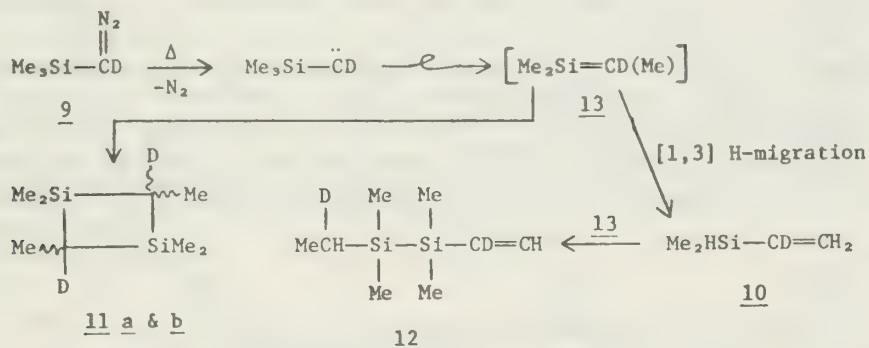
Evidence has also been adduced for the intermediacy of a silaolefin in the [3,3] sigmatropic rearrangement of propenylallyldimethylsilanes (7).¹⁰ It has been shown that these cis-(7a) and trans-(7b) isomers are interconvertible at temperatures above 800 K.



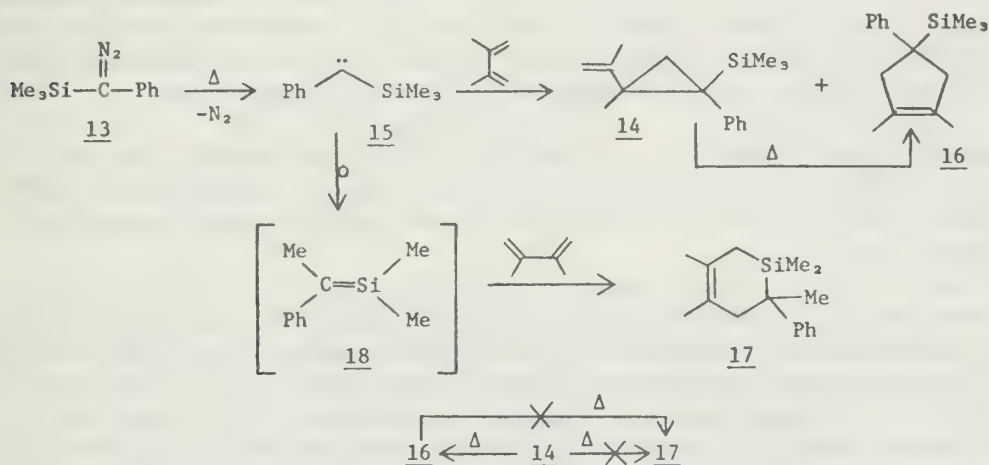
An investigation of the reaction kinetics of the thermolysis of 7a, studied over a temperature range of 800-860 K, gave Arrhenius parameters in close agreement with parameters obtained for the interconversion of the all-carbon analogues, cis- and trans-1,5-heptadiene.¹¹ The possibility of interconversion by a simple olefin isomerization was discounted by pyrolysis of cis- and trans-propenyltrimethylsilane which require a temperature 100° higher than for 7a and 7b. Thus, the interconversion of 7a and 7b was proposed to involve the silaethylene intermediate 8.

Products derived from intermediates containing Si-C double bonds generated from rearrangements in carbenes have been postulated. When trimethylsilyldiazomethane (9) is pyrolyzed, four products are observed: vinyltrimethylsilane (10), cis-(11a) and trans-(11b) 1,1,2,3,3,4-hexamethyl-1,3-disilacyclobutanes, and 3,3,4,4-tetramethyl-3,4-disila-

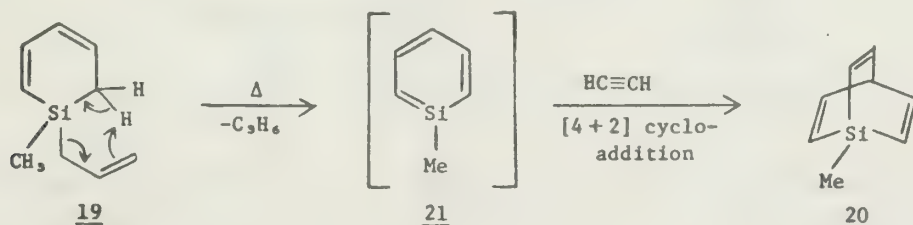
1-ene (12). By substitution of deuterium at the carbenic carbon, it was deduced from the position of the deuterium(s) in each product that a methyl migration from silicon to the carbenic carbon to form a silaethylene intermediate (13) must be responsible for the products obtained.



In another study, the pyrolysis of phenyltrimethylsilyldiazomethane (13) in the presence of 2,3-dimethyl-1,3-butadiene gave 14, the normal product of reaction of carbene 15 with a conjugated diene; 16, the product of thermal rearrangement of 14; and 17, the product from an apparent [2+4] cycloaddition of 18 with the diene.¹² Separate pyrolysis of 14 gave 16, but neither 14 nor 16 upon pyrolysis gave 17. This precludes the formation of 17 from further rearrangement of other products. Thus, evidence suggests strongly the intermediacy of silaolefin 18 derived from a rearrangement of carbene 15.

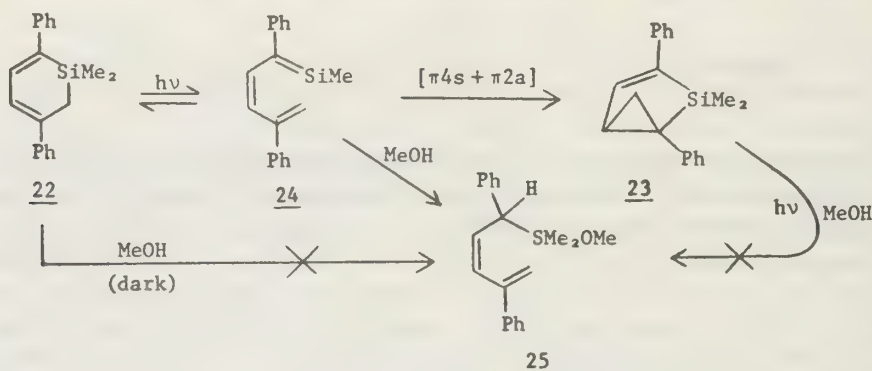


Silabenzenes have been pursued as possible compounds having a resonance stabilized Si-C double bond. When 1-methyl-1-allylsilacyclohexa-2,4-diene (19) is pyrolyzed in a stream of acetylene, 1-methyl-1-silabicyclo[2.2.2]octatriene (20) is formed.¹³ The formation of 20



is most economically explained by a retro-ene reaction to eliminate propene and form the intermediate 1-methylsilabenzene (21) which subsequently reacts with acetylene to give silabarrelene 20 by a [4 + 2] cycloaddition.

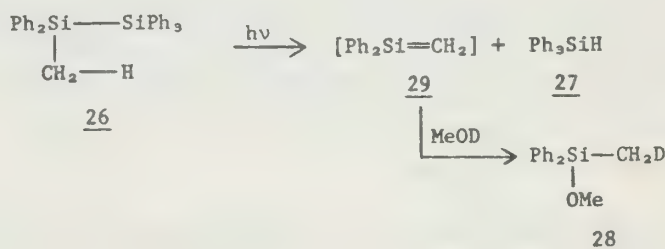
Photochemical Rearrangements. Double bonds between silicon and carbon have also been claimed to arise from photolytic rearrangements. Silicon-carbon double bonded intermediates have been implicated in the photoisomerization of 1,1-dimethyl-2,5-diphenyl-1-silacyclohexa-2,4-diene (22)^{14a} and 1,1,2,2-tetramethyl-3,6-diphenyl-1,2-disila-3,5-cyclohexa-diene.^{14b} Upon photolysis of 22, 23 is formed apparently from ring opening to the corresponding 1,3,5-silahexatriene 24 which subsequently ring closes by an allowed [$\pi 4s + \pi 2a$] cycloaddition. The intermediacy of



24 was further substantiated by photolysis of 22 in the presence of methanol which gave 25, the expected product from an addition of methanol across a Si-C double bond. Both 22 and 23 were inert to methanol without irradiation and 23 was inert with irradiation. These results provide substantial evidence for the formation of 24 as the reactive intermediate.

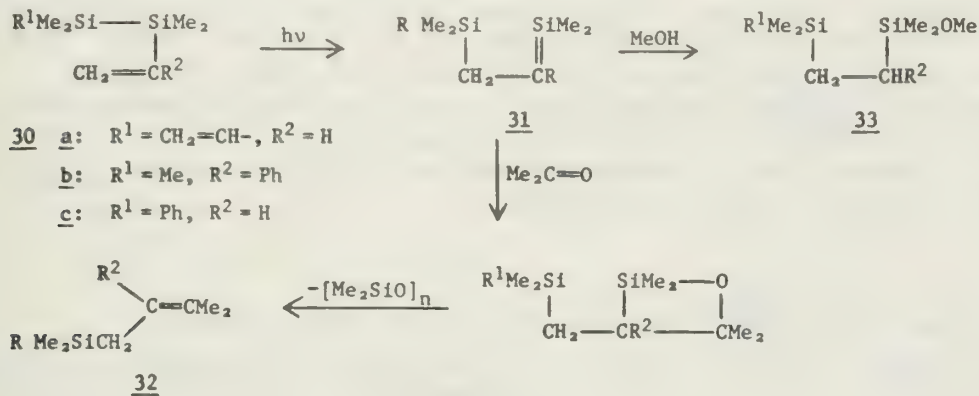
A number of photochemical studies of disilanes bearing various functionalities have been done. The postulation of intermediates containing Si-C double bonds have been made based upon product studies in trapping reactions.

An intermediate containing a Si-C double bond was proposed in the photolysis of pentaphenylmethylidisilane (26) in methanol-d. Triphenylsilane (27) and diphenylmethoxysilyldeuteriomethane (28) are observed.¹⁵ These products can be rationalized by an elimination of 27 to give 1,1-diphenylsilaethylene (29) which subsequently adds methanol to give 28, the expected product of addition of methanol-d across a Si-C double bond.

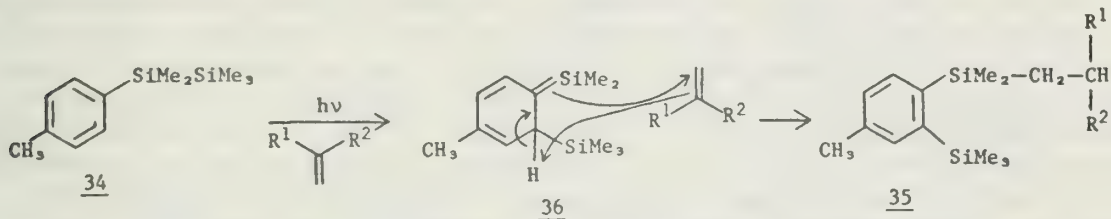


When vinylidisilanes, 30, are photolyzed in the presence of methanol or acetone, the products observed are from an apparent [1,3] migration of the silyl group to the terminal vinylic carbon with formation of the Si-C

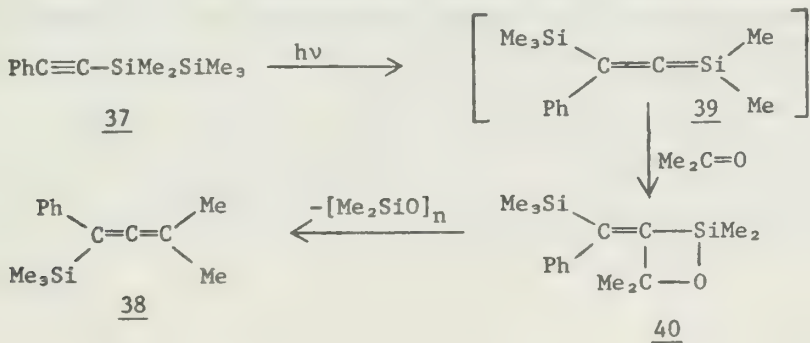
π -bonded intermediate 31, which can subsequently react with the added trapping reagent to give alkene 32 with acetone and methoxysilane 33 with methanol.^{16,17} These products are typical of those observed in the copyrolysis of ketones and alcohols with silacyclobutanes which implicates similar silaethylene intermediates in these reactions.



Aryl disilanes undergo a rearrangement similar to their vinyl analogues. When p-tolylpentamethyldisilane (34) is photolyzed in the presence of excess olefin, a 3-(trimethylsilyl)-4-(dimethylalkylsilyl) toluene 35 is formed.¹⁸ This can be rationalized by a $[\sigma_2s + \pi_2s + \pi_2s]$ addition of the olefin to dimethylsilene-2-(trimethylsilyl)-4-methyl-3,5-cyclohexadiene (36).

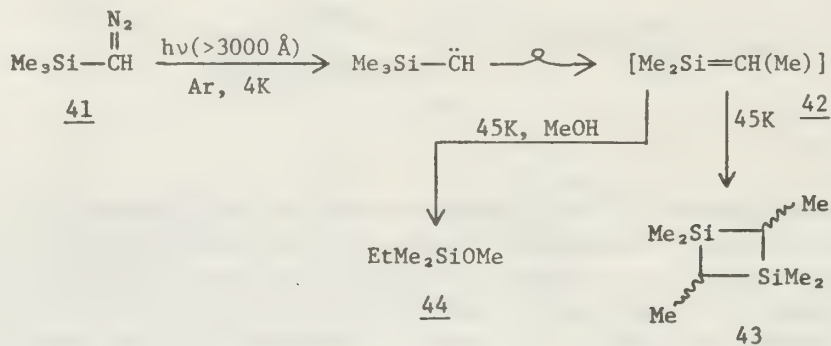


Alkynyl disilanes, also, undergo an apparent [1,3] migration of the terminal silyl group as do their vinyl and aryl analogues. When (penta-methyldisilanyl)phenylacetylene (37) is photolyzed in the presence of excess acetone, 1-trimethylsilyl-1-phenyl-3-methyl-1,2-propadiene (38) is formed. This product can be rationalized by cyclization of the acetone carbonyl with the Si-C double bond of the silaallene intermediate to form silaoxetane 39 followed by the loss of the Me₂SiO moiety.¹⁹



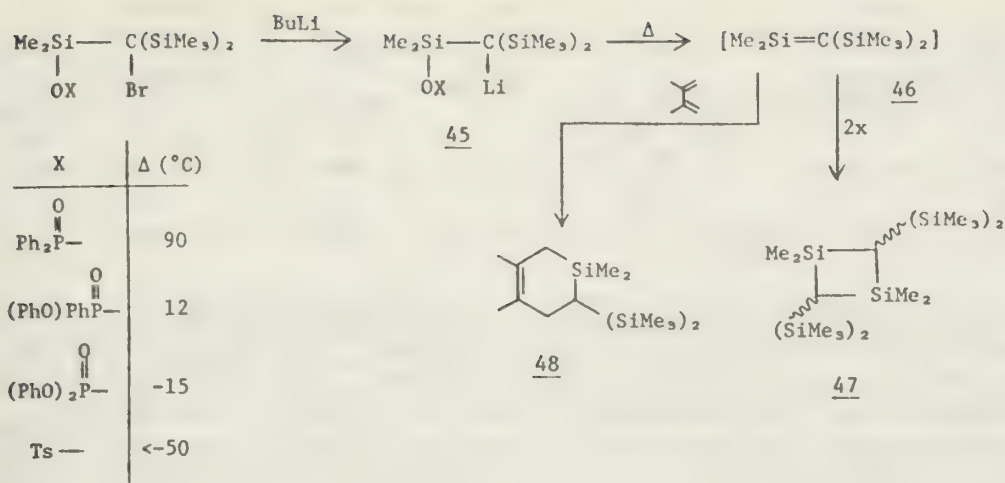
Isolation of reactive intermediates from photolysis of appropriate precursors in an argon matrix at very low temperatures has proven to be an effective method of studying reactive intermediates directly. Two groups almost simultaneously reported the observation of 2-methyl-2-sila-2-butene (41) under such conditions.²⁰

Photolysis of matrix isolated trimethylsilyldiazomethane (41) in argon at 4K with wavelength greater than 3000Å results in a rapid change of the infrared spectrum with formation of at least one new set of bands which are assigned to silaethylene 42. These new bands disappear upon warming to 45K and the spectrum of the dimerization product, 1,1,2,3,3,4-hexamethyl-1,3-disilacyclobutane (43) is observed. If methanol is added prior to warming, dimerization is suppressed and ethyl-dimethylmethoxysilane (44) is observed.

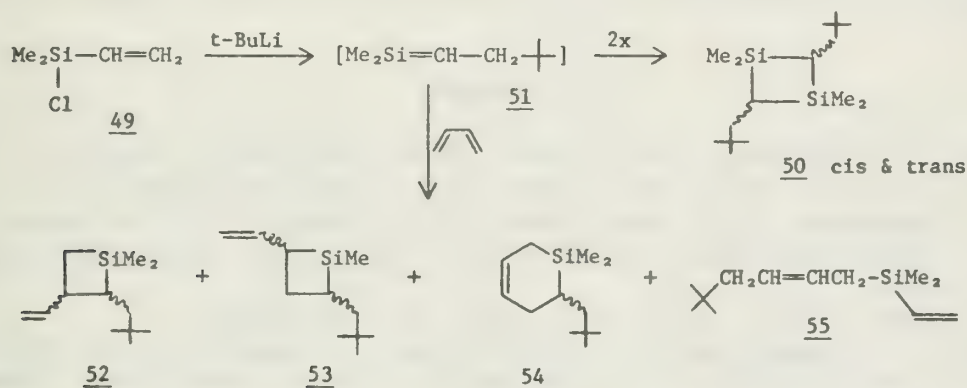


The infrared spectrum of the matrix isolated product of the photolysis of α -deuteroiteimethylsilyldiazomethane, presumably 3-deuterio-2-methyl-2-sila-2-butene, was determined in an attempt to assign absorptions of the olefinic hydrogen of 42. The C-H stretching frequency was unassignable. However, a strong bond at 641 cm^{-1} is shifted to 510 cm^{-1} in the deuterated intermediate. This absorption was assigned to the out-of-plane deformation of the lone vinylic hydrogen. Also, a new band at 1377 cm^{-1} which is absent in 41 was observed which could correspond to the bending of the C-methyl group. The similarities of the spectrum of the intermediate with that of trimethylethylene strongly suggest 42 is a planar molecule.

Elimination Reactions. Attempts have been made to generate intermediates bearing Si-C double bonds by elimination reactions. These have been claimed to be accessible from thermal eliminations in α -lithio siloxanes (45) in which the oxygen is part of a good leaving group. The temperature necessary to effect the elimination is dependent upon the leaving group ability. The silaethylene intermediate 46 and its dimerization product 47 were detected directly by mass spectrometry and 46 indirectly from trapping in [4 + 2] cycloaddition with 2,3-dimethylbutadiene to yield 48.²¹

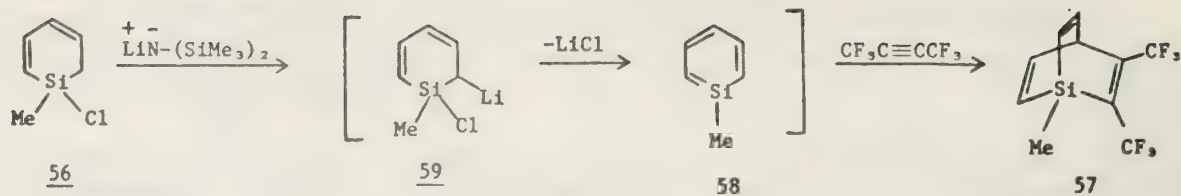


Another study involved the addition of t-butyllithium to vinylchloro-dimethylsilane (49).²² In the absence of trapping reagents, dimerization products, 50, were formed from the apparent silaolefin intermediate, 51. This intermediate can be explained by the addition of the anion to the terminal carbon of the vinyl group followed by displacement of chloride. In the presence of 1,3-butadiene, four products containing one butadiene unit are observed (52-55).



Products 52 and 53 are produced from an apparent [2+2] cycloaddition of silaolefin 51 with the butadiene and 53 from [4+2] cycloaddition. These strongly suggest the intermediacy of silaethylene 51 in these reactions since anionic routes would not lead to such products.

In another study, a silabenzene intermediate was postulated from the reaction of N-lithiohexamethyldisilazane with 1-methyl-1-chlorosilacyclohexa-2,4-diene (56) in the presence of excess perfluorobutyne.²³ The product, silabarralene 56, can be explained by the loss of LiCl from 59 to form silabenzene 58 followed by a [4+2] cycloaddition of 58 with the alkyne. From the inability of a ten-fold excess of chlorotrimethylsilane or methyl iodide to trap the reaction intermediate, an anionic mechanism from 59 to give products was discounted in favor of the silabenzene.



Molecular Orbital Calculations. Several molecular orbital calculation studies have been done for silaethylenes.²⁴ *Ab initio*, CNDO and Extended Hückel methods have all been employed. All qualitatively agree that silaethylenes have extremely polar Si-C π bonds, behaving as a siliconium-carbanion type species. A set of *ab initio* calculations^{24d} with an extended basis set and electron correlations included shows a surprisingly strong Si-C $p\pi$ - $p\pi$ bond for silaethylene. The π -bond strength was calculated to be ~ 46 kcal/mol or $\sim 70\%$ of the π -bond strength of ethylene, if the rotational barrier is accepted as a measure of π -bond strength. All sets of calculations show the inclusion of d-orbitals into the basis set is very important to the π -bond order.

These calculations show the considerably high reactivity of silaethylene intermediates can be attributed to the high polarity of the π -bond and to the rather low lying π antibonding orbital. The high reactivity is confirmed by the small barrier (< 14 kcal/mol) found for the dimerization of silaethylene, and also the large reaction energy (76 kcal/mol).

BIBLIOGRAPHY

1. (a) N. S. Nametkin, V. M. Vdovin, L. E. Gusel'nikov, and V. I. Zav'yslov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 584 (1966); (b) N. S. Nametkin, L. E. Gusel'nikov, V. M. Vdovin, P. L. Grinberg, V. I. Zav'yalov, and V. D. Oppengeim, *Dokl. Akad. Nauk SSSR*, **171**, 630 (1966).
2. H. M. Frey, *Advan. Phys. Org. Chem.*, **4**, 148 (1966).
3. (a) M. C. Flowers and L. E. Gusel'nikov, *J. Chem. Soc., B*, 419, 1396 (1968); (b) M. C. Flowers and L. E. Gusel'nikov, *Chem. Commun.*, 864 (1967).
4. P. S. Rotoli, M.S. Thesis, University of Rochester, 1963.
5. (a) N. S. Nametkin, L. E. Gusel'nikov, R. L. Ushakov, and V. M. Vdovin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1840 (1971); (b) N. S. Nametkin, L. E. Gusel'nikov, R. L. Ushakov, and V. M. Vdovin, *Dokl. Akad. Nauk SSSR*, **201**, 1365 (1971).
6. R. D. Bush, C. M. Galino, G. D. Homer, and L. H. Sommer, *J. Orgmet. Chem.*, **80**, 37 (1974).
7. D. N. Roark and L. H. Sommer, *J. Chem. Soc., Chem. Commun.*, 167 (1973).
8. R. D. Bush, C. M. Golino, D. N. Roark, and L. H. Sommer, *J. Orgmet. Chem.*, **59**, C17 (1973).
9. E. Block and L. K. Revelle, *J. Am. Chem. Soc.*, **100**, 1630 (1978).
10. J. Slutsky and H. Kwart, *J. Org. Chem.*, **38**, 3658 (1973).
11. H. M. Freg and R. K. Solly, *Trans. Farady Soc.*, 1858 (1968).
12. W. Ando, A. Sekizuchi, A. J. Rothchild, R. R. Gallucci, M. Jones, Jr., T. J. Barton, and J. A. Kilgour, *J. Am. Chem. Soc.*, **99**, 6995 (1977).
13. T. J. Barton and G. T. Burns, *J. Am. Chem. Soc.*, **100**, 5246 (1978).

14. (a) Y. Nakadaira, S. Kanouchi, and H. Sakarai, J. Am. Chem. Soc., 96, 5621 (1974); (b) Y. Nakadaira, S. Kanouchi, and H. Sakarai, ibid., 96, 5623 (1974).
15. P. Boudjouk, J. R. Roberts, C. M. Golino, and L. H. Sommer, J. Am. Chem. Soc., 94, 7926 (1972).
16. H. Sakurai, Y. Kamiyama, and Y. Nakadaira, J. Am. Chem. Soc., 98, 7424 (1976).
17. M. Ishikawa, T. Fuchikami, and M. Kumada, J. Orgmet. Chem., 117, C58 (1976).
18. (a) M. Ishikawa, T. Fuchikami, T. Sugaya, and M. Kumada, J. Am. Chem. Soc., 97, 5923 (1975); (b) M. Ishikawa, T. Fuchikami, and M. Kumada, J. Orgmet. Chem., 118, 139,155 (1976).
19. M. Sihikawa, T. Fuchikami, and M. Kumada, J. Am. Chem. Soc., 99, 245 (1977).
20. (a) O. L. Chapman, C. C. Chang, J. Kolc, M. E. Jund, and J. A. Lowe, J. Am. Chem. Soc., 98, 7844 (1976); (b) M. R. Chedekel, M. Skoglund, R. L. Kreeger, and H. Shechter, J. Am. Chem. Soc., 98, 7847 (1976).
21. N. Wiberg and G. Preiner, Angew. Chem., Int. Ed. Eng., 16, 328 (1977).
22. P. R. Jones and F. O. Lin, J. Am. Chem. Soc., 99, 2013, 8447 (1977).
23. T. J. Barton and D. S. Banasiak, J. Am. Chem. Soc., 99, 3199 (1977).
24. (a) M. D. Curtis, J. Orgmet. Chem., 60, 63 (1973); (b) R. Damrauer and D. R. Williams, J. Orgmet. Chem., 66, 241 (1974); (c) O. P. Strausz, L. Gammie, G. Theodorakoupoulos, P. G. Mezey, and I. G. Caizmadia, J. Am. Chem. Soc., 98, 1622 (1976); (d) R. Ahlrichs and R. Heinzmann, J. Am. Chem. Soc., 99, 7452 (1977).

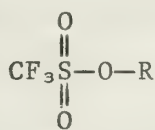
SYNTHETIC APPLICATIONS OF TRIFLONES AND TRIFLAMIDES

Reported by Steven R. Tarbox

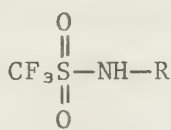
September 28, 1978

The sulfonyl group can be incorporated into an organic molecule as an electrophile or as a nucleophile. Moreover, this function as itself or bound to a heteroatom is an outstanding leaving group. This functional versatility makes the sulfonyl group an important tool in organic synthesis. The ability of the sulfonyl group to stabilize adjacent negative charge on carbon or a heteroatom and to activate double bonds for conjugate or cyclo additions is testimony to its appreciable electron withdrawing ability. The attachment of trifluoromethyl to sulfur provides the trifluoromethanesulfonyl (triflyl) group¹ which is one of the more potent electron withdrawing groups known, as evidenced by its strong deactivating effect in aromatic substitution² and its acidifying effect in triflic acid³ 1 (R = H).

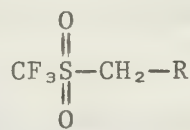
Organic compounds containing the trifluoromethanesulfonyl group can be divided into three classes depending on the atom bonded to the sulfonyl moiety. Attachment to oxygen gives the triflates⁴ 1; nitrogen provides triflamides⁵ 2; and carbon, triflones⁶ 3. Of the three, triflates have



1



2



3

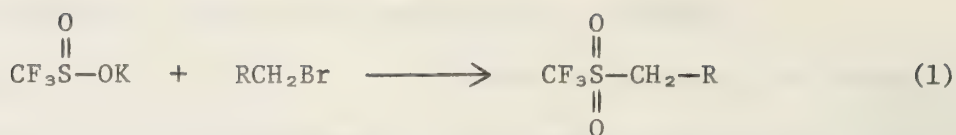
received the most attention to date primarily because of the behavior of the trifluoromethanesulfonate function as an outstanding leaving group.^{4,7} The synthetic applications of triflates are numerous⁸ and have been included in several reviews.^{1,2a}

In the present abstract, synthetic applications and the chemistry of triflones and triflamides is presented. The realized and potential applications of these two classes of compounds is substantial. Triflones and triflamides are readily formed; they provide powerful activation for a variety of synthetic steps and they are readily removed.

Triflones

Synthesis. The formation of triflones can be achieved by several pathways. A single preferred synthesis for all triflones does not appear to have been found, yet the versatility of methods available insures that a wide variety of triflones can be prepared.

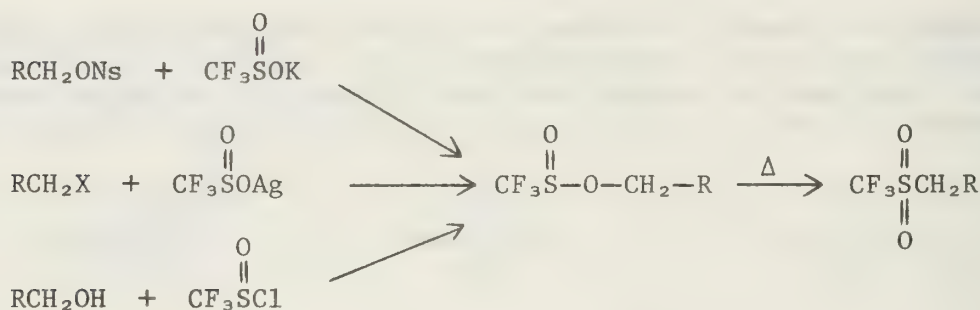
The triflinate anion is a nucleophilic source of the triflyl group. It reacts with primary alkyl bromides to give triflones by direct nucleophilic displacement (Eq. 1).^{1b,6} The utility of this method is limited to primary alkyl bromides due to the low nucleophilicity of the triflinate anion. An improved synthesis of methyl triflone relies on the pyrolysis of the alkylation product formed from potassium triflinate and t-butyl bromoacetate.⁹ Methyl triflone and bis(trifluoromethanesulfonyl)methane have also been synthesized by the reaction of methyl magnesium bromide with trifluoromethanesulfonyl fluoride.¹⁰ Other primary triflones are attainable through the reaction of organo-lithium reagents (n-butyl



lithium, ethyl lithium) with triflic anhydride or $\text{PhN}(\text{SO}_2\text{CF}_3)_2$.¹¹ Higher yields of desired product can be achieved in some instances with the reaction of organocopper lithium reagents ($n\text{-Bu}_2\text{CuLi}$) with $\text{PhN}(\text{SO}_2\text{CF}_3)_2$.

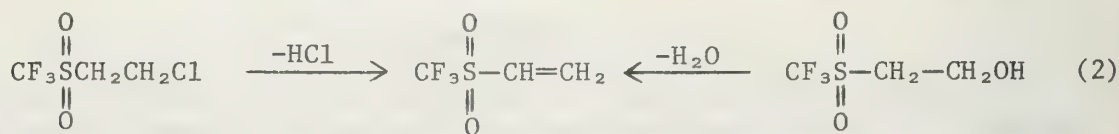
A general synthesis of primary triflones takes advantage of the well known thermal rearrangement of sulfinates to sulfones. Triflate esters which are readily available from both nucleophilic and electrophilic trifyl reagents similarly rearrange to yield triflones.^{6,9} (Scheme I)

Scheme I



Direct synthesis of tertiary triflones has not been achieved to date and only one successful direct synthesis of a secondary triflone has been realized. Hendrickson has succeeded in preparing sec-butyl triflone in moderate yields from sec-butyl lithium and either triflic anhydride or $\text{PhN}(\text{SO}_2\text{CF}_3)_2$.¹¹ Attempted syntheses of secondary triflones via triflate ester rearrangement have failed. The readily available secondary triflate esters undergo elimination to the olefin upon thermolysis.⁹

Vinyl triflones are generally available through syntheses of alkyl triflones which contain a β functionality that can be subsequently eliminated to form the olefin (Eq. 2).¹² Hendrickson has also used the



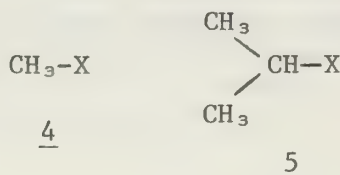
Mannich reaction of benzyl triflone with aldehydes to form vinyl triflones.⁶

Aryl triflones are synthesized by the oxidation of trifluoromethyl aryl sulfides,¹³ or by Freidal-Crafts acylation of aromatics with triflic anhydride- AlCl_3 .¹¹ Ditriflation in the latter case is not observed due to the strong deactivating effect of the trifyl group toward aromatic electrophilic substitution.² An acetylenic triflone has been synthesized from the corresponding lithium salt of phenyl acetylene and triflic anhydride.¹⁴

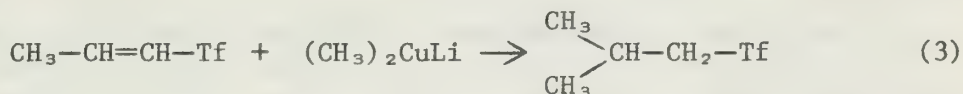
Uses. The synthetic utility of triflones lies in the strong electron withdrawing effect that the trifyl group has on the carbon atom bonded to sulfur. Hydrogens that are α to the trifyl group are among the more acidic carbon acids known (Table 1).¹⁵ Alkylations of triflone carbanions with carbonyl compounds,^{12a,16} organic halides,^{6,9,10b} and epoxides,^{10b} and Michael addition to olefins⁶ are typical of the reactions reported to date. Addition of one equivalent of base to the triflone before addition of the alkylating agent insures mono-alkylation as there is a significant increase in pKa as substitution of the α -carbon increases (Table 1).

Table 1. Carbon Acid pKa Values¹⁵

X	pKa of <u>4</u>	pKa of <u>5</u>
-NO ₂	17.2	16.9
-SO ₂ CF ₃	18.8	21.8
$\begin{array}{c} \text{O} \\ \parallel \\ \text{-CPh} \end{array}$	24.7	26.3
-SO ₂ Ph	29.0	>32

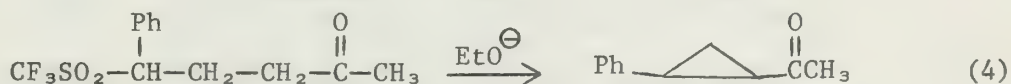


The electron withdrawing effect of the trifyl group makes vinyl triflones quite susceptible to conjugate addition. Yagupol'skii has reported the addition of a variety of nucleophiles, including aromatic thiols, phenols and amines to styryl and vinyl triflones.^{12b,17} Addition of lithium dimethyl cuprate to propenyl triflone has also been reported (Eq. 3).⁹

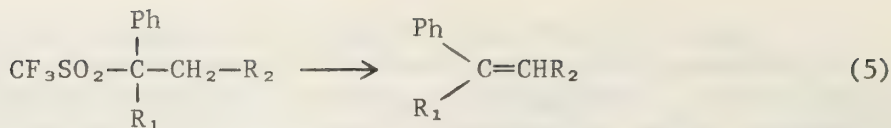


Vinyl triflones have been shown to be good dienophiles in the Diels-Alder reaction. Glass has studied the cycloaddition reaction of phenyl (trifluoromethanesulfonyl)acetylene with various dienes and found this reaction exceptionally facile despite the unfavorable steric effects.¹⁴

Removal. The potential synthetic application of triflones is enhanced by the ease and variety of methods by which the trifyl group is removed. Cleavage can be accomplished concurrent with a final carbon-carbon bond formation as in Eq. 4.⁶ Triflones with activated β protons



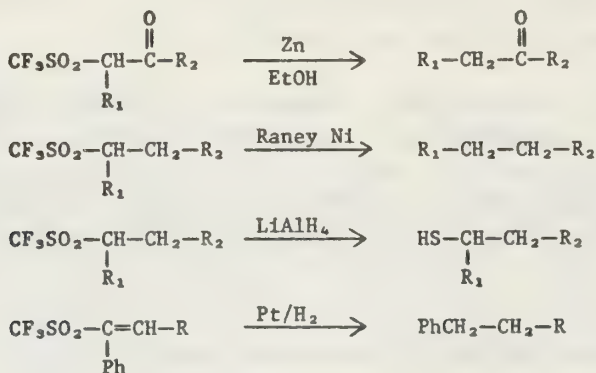
can be made to undergo [1,2] eliminations to give olefins and triflinic acid (Eq. 5). The substituted triflones, 6, thermally eliminate to yield the corresponding olefins quantitatively. Triflone 6c will also eliminate to chalcone under mild base conditions.⁶



- 6 a $\text{R}_1 = \text{H}, \text{R}_2 = \text{Ph}$
 b $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{Ph}$
 c $\text{R}_1 = \text{H}, \text{R}_2 = \overset{\text{O}}{\parallel} \text{CPh}$

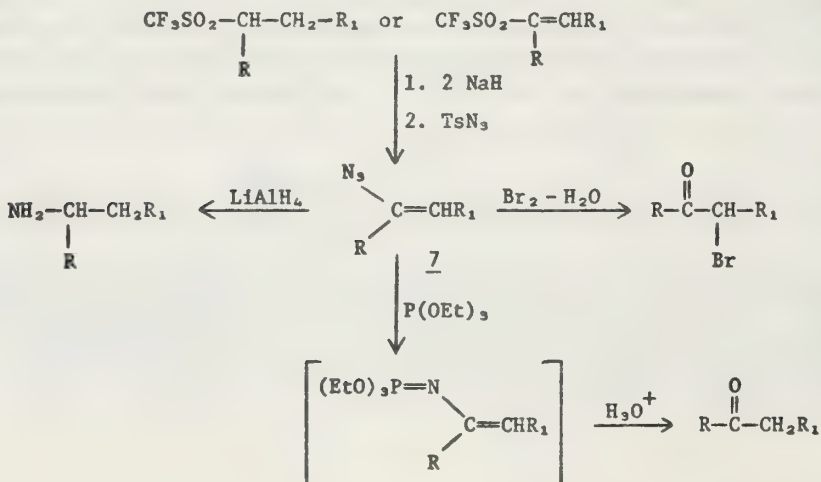
Reductive removal of the triflyl group can also be accomplished to yield the parent alkyl derivative or thiol. Compounds with a carbonyl function α to the triflyl group will undergo zinc reductive elimination quantitatively with no loss of carbonyl function. Triflones can be reduced with Raney nickel to yield the parent alkanes or with lithium aluminum hydride to yield the corresponding thiols. Platinum catalyzed hydrogenolysis of vinyl triflones is successful only when the triflyl group is benzylic.⁶ These reactions are summarized in Scheme II.

Scheme II



Oxidative removal of the triflyl group with a corresponding refunctionalization to either an amine or ketone has recently been demonstrated by Hendrickson.^{9,18} Triflones when treated with two moles of sodium hydride

Scheme III



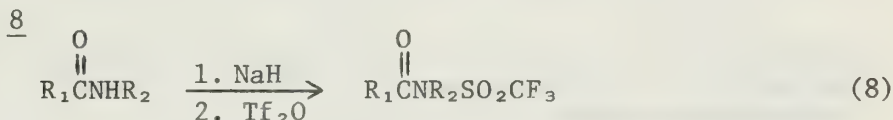
and tosyl azide yield the vinyl azides 7 which can be reduced to the amine⁹ or converted to an iminophosphorane and subsequently hydrolyzed to the ketone under mild acid conditions (Scheme III). Vinyl azides have also been converted to α -bromo ketones.¹⁹

Triflamides

Synthesis. Early syntheses of triflamides and trifluoromethanesulfonanilides usually suffered from poor yields and/or the lack of a readily available triflyl source.²⁰ Present constructions proceed in excellent yields (>90%) from the reaction of primary, secondary and aromatic amines²¹ with trifluoromethanesulfonic anhydride (Eq. 6).^{20b} Bis triflation is achieved by treating the amine with two equivalents of the anhydride. A milder and somewhat more selective triflyl source is phenyl triflimide 8 which has been found to triflylate primary aromatic amines but not secondary aromatic amines (Eq. 7).²² Amides are also easily triflylated by preforming the amide anion with NaH or t-butyl lithium and treating with triflic anhydride (Eq. 8).²¹



R_1 = aryl, alkyl
 R_2 = H, aryl, alkyl

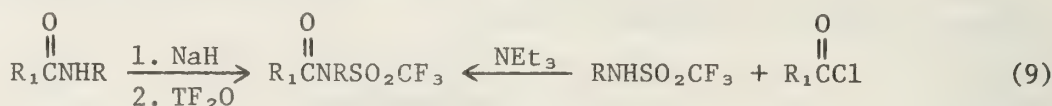


Uses. The realized utility of triflamides has been in the area of amine synthesis and amine protection. Acyl triflamides have also been shown to act as excellent acylating agents.²² Primary triflamides are quite acidic (pK_a 's = 6 ~ 10)²³ and are potentially good leaving groups for the second step of an addition elimination sequence. Simple nucleophiles thus will react with acyl triflamides to afford acylated products in high yield (Table 2). These and other acyl triflamides are prepared from

Table 2. Acyl Triflamides as Acylating Agents²²

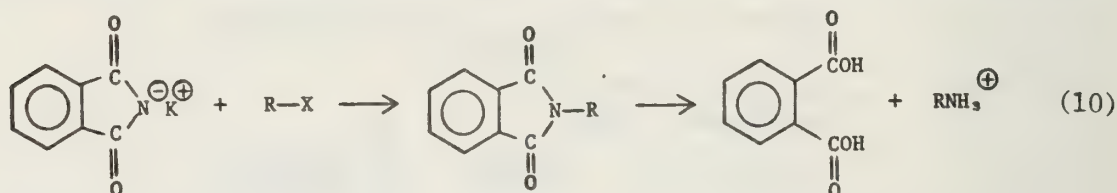
Nucleophile	Triflamide	Product	% Yield
PhNH ₂	$\begin{array}{c} \text{O} \quad \text{Ph} \\ \quad \\ \text{CH}_3\text{C}-\text{N}-\text{SO}_2\text{CF}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{PhNHCCH}_3 \end{array}$	92
PhNH ₂	$\begin{array}{c} \text{O} \quad \text{Ph} \\ \quad \\ \text{PhC}-\text{N}-\text{SO}_2\text{CF}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{PhNHCPh} \end{array}$	93
PhCH ₂ NH ₂	$\begin{array}{c} \text{O} \quad \text{Ph} \\ \quad \\ \text{CH}_3\text{C}-\text{N}-\text{SO}_2\text{CF}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{PhCH}_2\text{NHCCH}_3 \end{array}$	97
PhCH ₂ NH ₂	$\begin{array}{c} \text{O} \quad \text{Ph} \\ \quad \\ \text{PhC}-\text{N}-\text{SO}_2\text{CF}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{PhCH}_2\text{NHCPh} \end{array}$	98

the reaction of an acid chloride with some triflamide or by the reaction of a preformed amide anion with triflic anhydride (Eq. 9).



The use of the trifyl function as an amine protecting group is advantageous due to the ease with which the triflamide is formed and cleaved.^{21,24} Amines are typically transformed to the triflamides with triflic anhydride in high yield (Eq. 6). Deprotection of secondary triflamides is quantitatively afforded through reductive removal by lithium aluminum hydride while primary triflamides require sodium bismethoxyethoxy aluminum hydride ($\text{NaAlH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, Red-Al²⁵).

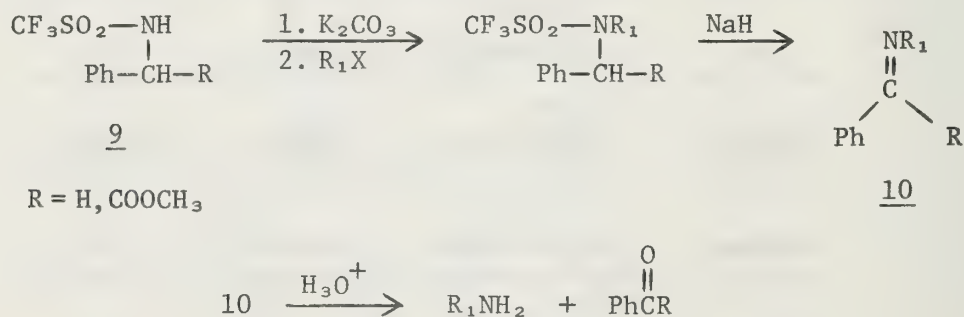
The Gabriel synthesis is the classical method of primary amine synthesis (Eq. 10).²⁶ The phthaloyl group prevents dialkylation but can be a source of contamination in itself upon hydrolysis or hydrazinolysis



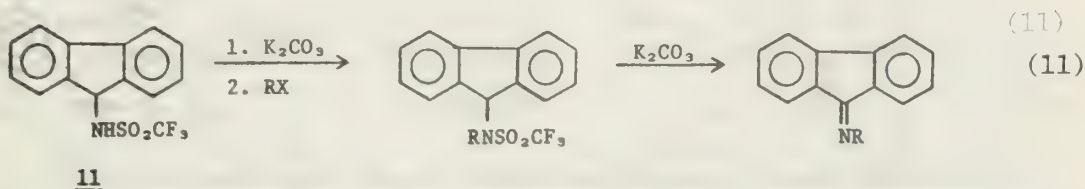
as phthalate. Instability of certain R groups to the generally harsh hydrolysis or hydrazinolysis conditions necessary to free the amine also constitutes another drawback.

A Gabriel parallel for the synthesis of primary amines has been developed utilizing alkylation of triflamide anions (Scheme IV).^{21,24,27} Mild alkylation and cleavage conditions circumvent problems normally associated with the Gabriel synthesis. A monosubstituted triflamide 9 is used that prevents dialkylation which occurs readily if the unsubstituted triflamide is used. Substitution of the triflamide 9 is chosen such that the substituent activates protons α to nitrogen which then can be removed in base to effect a [1,2] elimination to the imine 10 and triflate anion. Mild acid hydrolysis of the imine 10 then yields the primary amine in 60-90% overall yield.

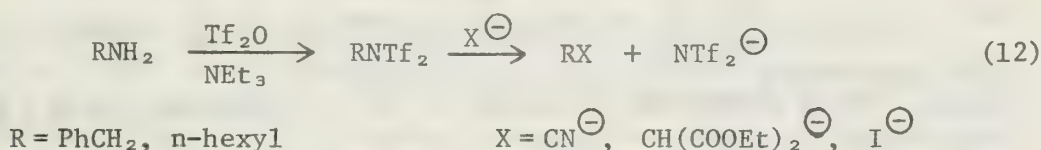
Scheme IV



9-Fluorenyl triflamide 11 has also been reported as a Gabriel reagent.^{27,1a,b} The critical elimination to the imine occurs under mildly basic conditions (Eq. 11) and the fluorenyl function is less labile than the carbomethoxy group.



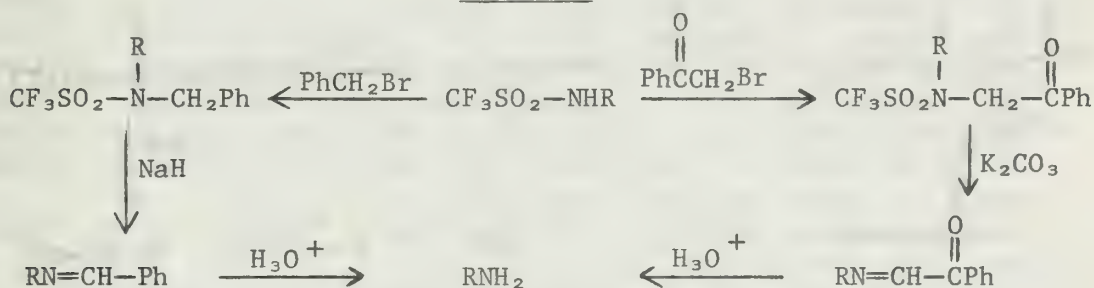
Bis trifylation of amines enhances the ability of the triflimide anion to act as a leaving group. Glass²⁸ has demonstrated simple nucleophilic displacement of $(\text{CF}_3\text{SO}_2)_2\text{N}^-$ by cyanide, malonate and halide nucleophiles from benzyl and n-hexyl bis triflimide (Eq. 12).



Bis triflimides also act as a milder and more convient trifylating agent than triflic anhydride. The non-hygroscopic reagent $\text{PhN}(\text{SO}_2\text{CF}_3)_2$ has been applied²² to several nitrogen and oxygen nucleophiles that gave poor trifylations with triflic anhydride or other trifylating agents such as trifyl imidazole.²⁹

Removal. Removal of the trifyl function from primary amines is achieved by two methods. Besides reductive removal with specific hydride reducing agents, primary triflamides can be phenacylated (Scheme V)²¹ to give triflamides with activated α -protons. Treatment with mild base affords the imine which is then hydrolyzed with acid. Benzylation of primary triflamides results in compounds that eliminate to the imine only with strong base.

Scheme V



Miscellaneous. Acyl trifyl hydrazines have been shown to assist in the conversion of alkyl halides to acyl hydrazones (Scheme VI).³⁰ Alkylation of the acyl trifyl hydrazine in mild base yields the adduct 12 which eliminates and tautomerizes to the acyl hydrazone 13 and triflimide anion. Subsequent hydrolysis yields the carbonyl compound. Transformations are limited to primary halides, nosylates and activated secondary halides.



BIBLIOGRAPHY

1. For recent reviews of trifluoromethanesulfonyl chemistry see:
(a) J. B. Hendrickson, D. D. Sternbach, and K. W. Bair, *Accts. Chem. Res.*, 10, 306 (1977); (b) J. B. Hendrickson, K. W. Bair, R. Bergeron, A. Giga, P. L. Skipper, D. D. Sternbach, and J. A. Wareing, *Org. Prep. Proced. Int.*, 9, 173 (1977); (c) R. D. Howells and J. D. McCown, *Chem. Rev.*, 69 (1977).
2. (a) A. Senning, *Chem. Rev.*, 385 (1965); (b) W. A. Sheppard, *J. Am. Chem. Soc.*, 85, 1314 (1963).
3. (a) T. Gramstad, *Tidsskr. Kjem., Bergues. Metall.*, 19, 62 (1959); *Chem. Abstr.*, 54, 12739c (1960); (b) A. Engelbrecht and B. M. Rode, *Monatsh. Chem.*, 103, 1315 (1972); (c) E. A. Robinson, *Can. J. Chem.*, 39, 247 (1974); (d) D. G. Russell and J. B. Senior, *Can. J. Chem.*, 52, 2975 (1974); (e) G. M. Kramer, *J. Org. Chem.*, 40, 298 (1975); (f) G. M. Kramer, *J. Org. Chem.*, 40, 302 (1975); (g) R. V. Gillespie and T. E. Peel, *Adv. Phys. Org. Chem.*, 9, 1 (1971).
4. A. Streitwieser, Jr., C. L. Wilkins, and E. Kielman, *J. Am. Chem. Soc.*, 90, 1598 (1968).
5. J. B. Hendrickson, R. Bergeron, A. Giga, and D. D. Sternbach, *J. Am. Chem. Soc.*, 95, 3412 (1975).
6. J. B. Hendrickson, A. Giga, and J. A. Wareing, *J. Am. Chem. Soc.*, 96, 2275 (1976).
7. (a) T. E. Dueber, P. J. Strong, W. D. Pfeifer, R. H. Summerville, M. A. Imhoff, P. von R. Schleyer, K. Hummell, S. Bocher, C. E. Harding, and M. Hanack, *Angew. Chem. Int. Ed.*, 9, 521 (1970); (b) P. J. Stang and M. G. Mangum, *J. Am. Chem. Soc.*, 97, 6478 (1975); (c) R. L. Hansen, *J. Org. Chem.*, 30, 4322 (1965); (d) T. MunSu, W. F. Sliwinski, and P. von R. Schleyer, *J. Am. Chem. Soc.*, 91, 5386 (1969).

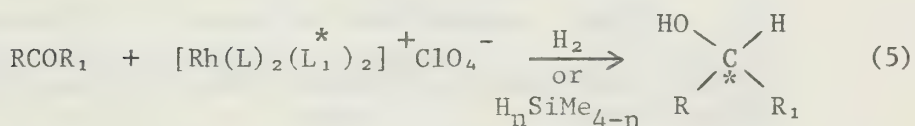
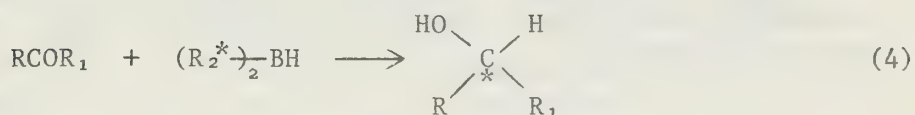
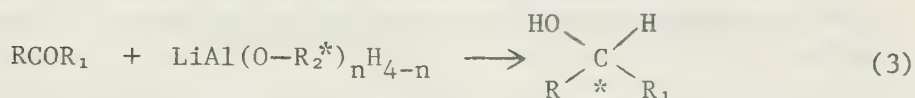
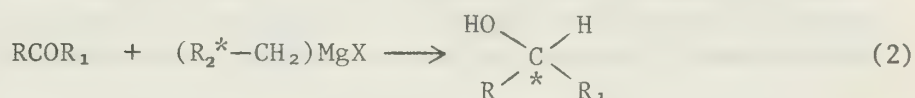
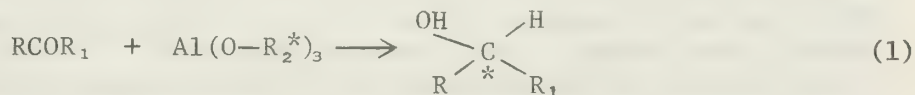
8. See for example: (a) E. Vedejs, P. A. Engler, and M. J. Mullins, *J. Org. Chem.*, 42, 3109 (1977); (b) R. L. Shone, *Tetrahedron Lett.*, 993 (1977); (c) J. B. Hendrickson and S. M. Schwartzman, *ibid.*, 273 (1975); (d) J. B. Hendrickson and S. M. Schwartzman, *ibid.*, 277 (1975); (e) J. Burdon and U. C. R. McLoughlin, *Tetrahedron*, 21, 1 (1965).
9. J. B. Hendrickson and P. L. Skipper, *Tetrahedron*, 32, 1627 (1976).
10. (a) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 4069 (1957); (b) R. J. Koshar and R. A. Mitsch, *J. Org. Chem.*, 38, 3358 (1973).
11. J. B. Hendrickson and K. W. Bair, *J. Org. Chem.*, 42, 3875 (1977).
12. (a) L. M. Yagupol'skii and A. G. Panteleimonov, *Zh. Obshch. Khim.*, 36, 416 (1966); (b) I. M. Krunyants, I. N. Rozhkov, A. M. Alexsandrov, and L. M. Yagupol'skii, *Zh. Obshch. Khim.*, 37, 1277 (1967).
13. (a) L. M. Yagupol'skii and B. E. Gruz, *Zh. Obshch. Khim.*, 31, 1315 (1961); (b) D. C. Remy, K. E. Rittle, C. A. Hunt, and M. B. Freedman, *J. Org. Chem.*, 41, 1644 (1976).
14. R. S. Glass and D. L. Smith, *J. Org. Chem.*, 39, 3712 (1974).
15. F. G. Bordwell, N. R. Vanier, W. S. Matthews, J. B. Hendrickson, and P. L. Skipper, *J. Am. Chem. Soc.*, 97, 7160 (1975).
16. L. M. Yagupol'skii, A. G. Panteleimonov and U. V. Orda, *Zh. Obshch. Khim.*, 34, 3456 (1964).
17. A. G. Panteleimonov and L. M. Yagupol'skii, *Zh. Obshch. Khim.*, 36, 1976 (1966).
18. J. B. Hendrickson, K. R. Bair, and P. M. Keehn, *J. Org. Chem.*, 42, 2935 (1977).
19. A. Hassner and A. B. Levy, *J. Am. Chem. Soc.*, 93, 5469 (1971).
20. (a) T. Gramstad and R. W. Haszeldine, *J. Chem. Soc.*, 173 (1957); (b) J. Burdon, I. Farazmand, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2574 (1957); (c) M. I. Dronkina, G. P. Syrova, L. Z. Gandel'sman, Yu. N. Sheinker, and L. M. Yagupol'skii, *Zh. Organ. Khim.*, 8, 9 (1972); (d) L. Z. Gandel'sman, M. I. Dronkina, V. P. Nazaretyan, and L. M. Yagupol'skii, *Zh. Organ. Khim.*, 8, 1659 (1972); (e) L. M. Yagupol'skii, L. Z. Gandel'sman, and V. P. Nazaretyan, *Zh. Organ. Khim.*, 10, 889 (1974).
21. J. B. Hendrickson, R. Bergeron, A. Giga, and D. Sternbach, *J. Am. Chem. Soc.*, 95, 3412 (1973).
22. J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, 4607 (1973).
23. (a) R. D. Trepka, J. K. Harrington, and J. W. Belisle, *J. Org. Chem.*, 39, 1094 (1974); (b) F. G. Bordwell and D. Algrim, *J. Org. Chem.*, 41, 2507 (1976).
24. J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, 3839 (1973).
25. E. H. Gold and E. Babad, *J. Org. Chem.*, 37, 2208 (1972).
26. M. S. Gibson and R. W. Bradshaw, *Angew. Chem. Int. Ed.*, 7, 919 (1968).
27. J. B. Hendrickson, R. Bergeron, and D. D. Sternbach, *Tetrahedron*, 31, 2517 (1975).
28. (a) R. S. Glass, *Chem. Commun.*, 1546 (1971); (b) R. S. Glass and R. J. Swedo, *J. Org. Chem.*, 43, 2291 (1978).
29. F. Effenberger and K. E. Mack, *Tetrahedron Lett.*, 3947 (1970).
30. J. B. Hendrickson and D. D. Sternbach, *J. Org. Chem.*, 40, 3450 (1975).

ASYMMETRIC REDUCTION OF CARBONYL COMPOUNDS

Reported by James L. Schreiner

October 2, 1978

Optically active compounds are of interest to both mechanistic and synthetic work. The asymmetric reduction of a carbonyl compound to a chiral alcohol is one of the most important routes to optically active materials. The chiral alcohols are useful as such and can be modified to form other chiral functional groups. There a variety of methods to accomplish stereoselective reduction of carbonyl compounds.



The Meerwein-Pondorf-Verley (MPV) reduction (Eq. 1) involves the conversion of a carbonyl compound to an alcohol by (formally) a hydride transfer from the aluminum alkoxide.¹⁻⁴ Asymmetric induction is achieved when chiral alcohols are used to prepare the aluminum alkoxides. Many different chiral alcohols and metal ions have been used in asymmetric MPV reductions.⁵⁻¹⁰

Asymmetric formation of alcohols from carbonyl compounds has been reported in Grignard reactions (Eq. 2). If a chiral halide, in which the chiral center is not the carbon containing the halogen, is used to prepare the Grignard reagent, asymmetric induction occurs in the subsequent reduction.^{9,11-21}

Non-stereoselective reduction of carbonyl compounds by metal hydrides is a well known reaction. Initial partial decomposition of a metal hydride by a chiral substrate affords an active species that subsequently gives chiral alcohols as its product from reaction with carbonyl compounds (Eq. 3).²²⁻³⁴ The use of chiral organoboranes to asymmetrically hydroborate olefins is known.³⁵ The application of chiral organoboranes to the asymmetric reduction of ketones has been studied (Eq. 4).³⁶⁻⁴¹

Transition metal complexes have been of increasing use in organic synthesis. Complexes prepared using chiral ligands has prompted their use in the stereoselective reduction of carbonyl compounds by either hydrosilylation⁴² or hydrogenation (Eq. 5).⁴³⁻⁴⁵

Since NaBH_4 is insoluble in non-polar organic solvents, but soluble in water, the use of a phase transfer catalyst to facilitate reduction of ketones in the non-polar solvent is feasible. The use of a chiral phase transfer catalyst has been shown to induce asymmetry in the reduction of carbonyl compounds.⁴⁶ Lecithin was also used as a chiral phase transfer catalyst.⁴⁷ A suspension of actively fermenting yeast has also been used for stereoselective reductions.^{48,49}

Biological systems are well known to produce or utilize one stereoisomer in asymmetric reactions, particularly reduction by NADH .⁵⁰⁻⁵² The biomimetic asymmetric reduction of carbonyl compounds has been investigated using a model NAD(P)H compound.⁵³⁻⁶⁴ The Hantzsch esters, being similar to the model NAD(P)H compounds, have also been used to induce asymmetry in the reduction of α -ketoesters.⁶⁵ Rather than use a model system for the reductions, asymmetric microbial reduction of hydroaromatic ketones has been recently investigated.^{66,67}

Catalytic asymmetric reduction of ketones has been reported using cathodic reduction at a mercury electrode in the presence of a chiral alkaloid.⁶⁸⁻⁷¹

Table 1 provides a comparative summary of the amount of asymmetric induction reported for reduction of acetophenone and trifluoroacetophenone by various methods.

Table 1. Asymmetric Reductions of Acetophenone and Trifluoroacetophenone

Reagent	Ketone	% Yield ^a	% ee ^b	Configuration ^c	Reference
LAH : oxazoline 1 : 2	PhCOCH_3	80	65	R	29
BH_3 — L-Leucine methyl ester	"	100 ^d	17	S	37
LAH: (+)-(2S,3R)-4-dimethyl- amino-3-methyl-1,2-diphenyl- 2-butanol 1 : 2	"	100 ^d	40	R	31
$[\text{Rh}(\text{COD})(\text{PNNP})]^+\text{ClO}_4^-/\text{H}_2$	"	72 ^e	16.7	R	44
tris-[(S)-2-methylbutyl]aluminum	"	94 ^e	5.9 ^f	S	14
Lecithin	"	90 ^e	—8	R	47
Cathodic (Cinchonine)	"	20	9.7	S	69
Microbial (Cryptococcus macrans)	"	90	~100	S	66
Lithium β -isopinocampheyl-9- borabicyclo[3.3.1]nonyl hydride	"	70-80	17	R	39
Yeast	PhCOCF_3	>80 ^h	44	R	49
tris-[(S)-2-methylbutyl]aluminum	"	100	6.0 ^f	S	14
(R)-1-benzyl-1,4-dihydronicotin- amide	"	58	16	S	54
(R)-isoborneoxy magnesium bromide	"	60	2.0	R	6
(R)-menthoxy aluminum dichloride	"	50	77.0	S	6
(R)-borneoxy magnesium bromide	"	50	23.3	S	6
(S)-2-methyl-1-butoxy magnesium bromide	"	—	5.0	R	8

Footnotes to Table 1:

^aisolated yield unless otherwise noted

^b% optical purity converted to % ee

^cconfiguration of carbinol in excess

^dYield by GLC

^e% conversion

^fadjusted for optical purity of aluminum reagent

^gobserved rotation of +0.21° $\lambda = 350\text{nm}$

^hreported after 3 days

BIBLIOGRAPHY

1. A. L. Wilds, *Org. Reactions*, 2, 178 (1944).
2. T. Bersin in "Neuere Methoden der Präparativen Organischen Chemie", ed. W. Forest, Berlin: Verlag Chemie, GmbH, 1944, pp. 137-154; English translation and revision, E. R. Webster and J. V. Crawford, "Newer Methods of Preparative Organic Chemistry", Interscience Pub., New York, 1948, pp. 125-153.
3. C. G. Screttas and C. T. Cazianis, *Tetrahedron*, 34, 933 (1978).
4. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Inc., 1971, pp. 160-165, and references therein.
5. For a review of references to 1971, see ref. 4, pp. 165-177, and references therein.
6. D. Nasipuri and P. K. Bhattacharya, *J. Chem. Soc., Perkin Trans. I*, 576 (1976).
7. L. Menicagli, G. P. Giacomelli, and L. Lardicci, *J. Organomet. Chem.*, 50, C15 (1973).
8. J. D. Morrison and R. W. Ridgway, *J. Org. Chem.*, 39, 3107 (1974).
9. R. Ridgway, Ph.D. thesis, Univ. of New Hampshire, 1970.
10. O. Cervinka, O. Belovsky, A. Fabryova, V. Dudek, and K. Groham, *Coll. Czech. Chem. Commun.*, 32, 2618 (1967).
11. For a review of references to 1971, see ref. 4, pp. 177-202, and references therein.
12. J. D. Morrison, J. E. Tomaszewski, H. S. Mosher, J. Dale, D. Miller, and R. L. Elsenbaumer, *J. Am. Chem. Soc.*, 99, 3167 (1977).
13. L. Lardicci, G. P. Giacomelli, and R. Menicagli, *Tetrahedron Lett.*, 687 (1972).
14. G. Giacomelli, R. Menicagli, and L. Lardicci, *J. Org. Chem.*, 38, 2370 (1973).
15. G. Giacomelli, R. Menicagli, and L. Lardicci, *J. Org. Chem.*, 39, 1757 (1974).
16. L. Lardicci and G. Giacomelli, *J. Chem. Soc., Perkin Trans. I*, 337 (1974).
17. G. P. Giacomelli, R. Menicagli, and L. Lardicci, *J. Am. Chem. Soc.*, 97, 4009 (1975).
18. G. Giacomelli, L. Lardicci, and A. M. Caporusso, *J. Chem. Soc., Perkin Trans. I*, 1795 (1975).
19. G. Giacomelli, R. Menicagli, A. M. Caporusso, and L. Lardicci, *J. Org. Chem.*, 43, 1790 (1978).

20. R. A. Kretchmer, *J. Org. Chem.*, 37, 801 (1972).
21. O. Cervinka and J. Fusek, *Coll. Czech. Chem. Commun.*, 38, 441 (1973).
22. For a review of references to 1971, see ref. 4, pp. 202-215, references therein.
23. J. D. Evans, S. R. Landor, and J. P. Regan, *J. Chem. Soc., Perkin Trans. I*, 552 (1974).
24. N. Baggett and P. Stribblehill, *J. Chem. Soc., Perkin Trans. I*, 1123 (1977).
25. T. Mukaiyama, M. Asami, J. Hanna, and S. Kobayashi, *Chem. Lett.*, 783 (1977).
26. A. S. Angeloni, S. Marzocchi, and G. Scapini, *Gazz. Chim. Ital.*, 107, 421 (1972).
27. S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Am. Chem. Soc.*, 94, 9254 (1972).
28. R. S. Brinkmeyer and V. M. Kapoor, *J. Am. Chem. Soc.*, 99, 8339 (1977).
29. A. I. Meyers and P. M. Kendall, *Tetrahedron Lett.*, 1337 (1974).
30. G. M. Giongo, F. DiGregorio, N. Palladino, and W. Marconi, *Tetrahedron Lett.*, 3195 (1973).
31. S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, 38, 1870 (1973).
32. E. D. Lund and P. E. Shaw, *J. Org. Chem.*, 42, 2073 (1977).
33. R. Andrisano, A. S. Angeloni, and S. Marzocchi, *Tetrahedron*, 29, 913 (1973).
34. S. Yamaguchi and K. Kabuto, *Bull. Chem. Soc. Jap.*, 50, 3033 (1977).
35. For a discussion, see ref. 4, p. 220.
36. For a review of references to 1971, see ref. 4, pp. 215-218, and references therein.
37. M. F. Grundon, D. G. McCleery, and J. W. Wilson, *Tetrahedron Lett.*, 295 (1976).
38. H. C. Brown and A. K. Mandal, *J. Org. Chem.*, 42, 2996 (1977).
39. S. Krishnamurthy, F. Vogel, and H. C. Brown, *J. Org. Chem.*, 42, 2534 (1977).
40. M. M. Midland, A. Tramontano, and S. A. Zderic, *J. Am. Chem. Soc.*, 99, 5211 (1977).
41. M. F. Grundon, W. A. Khan, D. R. Boyd, and W. R. Jackson, *J. Chem. Soc., C*, 2557 (1971).
42. Garret D. Figuly, *Organic Seminar Abstract, Univ. of Illinois*, Nov. 14, 1977.
43. M. Tanaka, Y. Watanabe, T. Mitsudo, H. Iwane, and Y. Takegami, *Chem. Lett.*, 239 (1973).
44. M. Fiorini, F. Marcati, and G. M. Giongo, *J. Molecular Catalysis*, 3, 385 (1977).
45. I. Ojima, T. Kogure, T. Terasaki, and K. Achiuro, *J. Org. Chem.*, 43, 3444 (1978).
46. J. P. Masse and E. R. Parayre, *Chem. Commun.*, 438 (1976).
47. T. Doiuchi and Y. Minoura, *Isr. J. Chem.*, 15, 84 (1977).
48. D. D. Ridley and M. Stralow, *Chem. Commun.*, 400 (1975).
49. M. Bucciarelli, A. Forni, I. Moretti, and G. Torre, *Chem. Commun.*, 456 (1978).
50. J. Everse and N. O. Kaplan, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 37, 61 (1973).
51. R. Bentley, "Molecular Asymmetry in Biology", Vol. 2, Academic Press, New York, 1970, p. 50.
52. B. L. Vallee and W. E. C. Wacker, *J. Am. Chem. Soc.*, 78, 1771 (1956).
53. Y. Ohnishi, M. Kagami, and A. Ohno, *J. Am. Chem. Soc.*, 97, 4766 (1975).
54. Y. Ohnishi, T. Numakunai, and A. Ohno, *Tetrahedron Lett.*, 3813 (1975).
55. Y. Ohnishi, T. Numakunai, T. Kimura, and A. Ohno, *Tetrahedron Lett.*, 2699 (1976).

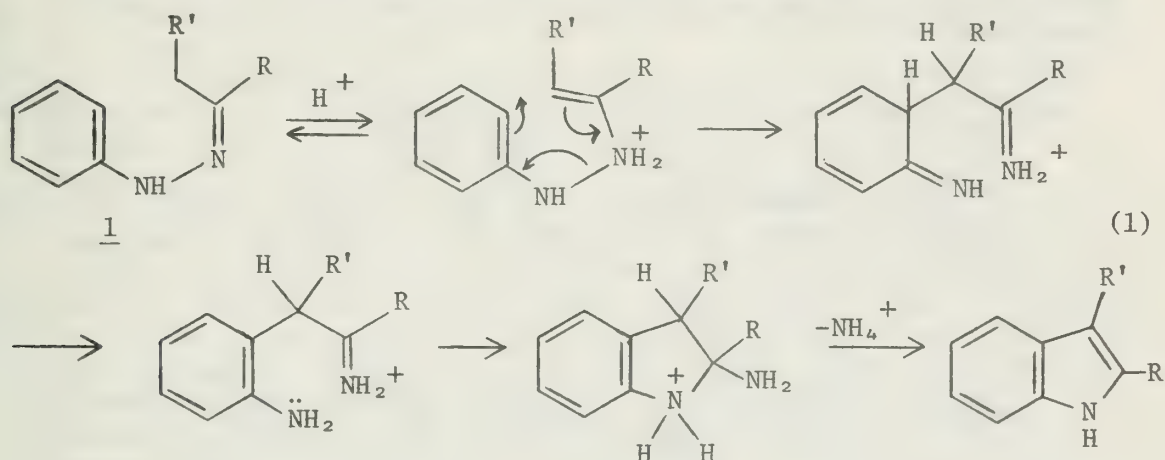
56. A. Ohno, H. Yamamoto, T. Kimura, S. Oka, and Y. Ohnishi, *Tetrahedron Lett.*, 4585 (1976).
57. A. Ohno, T. Kimura, S. G. Kim, H. Yamamoto, S. Oka, and Y. Ohnishi, *Bioorganic Chem.*, 6, 21 (1977).
58. A. Ohno, T. Kimura, S. G. Kim, H. Yamamoto, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Jap.*, 50, 1535 (1977).
59. A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, *Chem. Commun.*, 328 (1978).
60. A. Ohno, T. Kimura, S. Oka, and Y. Ohnishi, *Tetrahedron Lett.*, 757 (1978).
61. H. J. van Ramesdonk, J. W. Verhoeven, U. K. Pandit, and Th. J. de Boer, *Rec. Trav. Chim.*, 97, 195 (1978).
62. A. Ohno, H. Yamamoto, T. Okamoto, S. Oka, and Y. Ohnishi, *Chem. Lett.*, 65 (1978).
63. T. Endo, Y. Hayashi, and M. Okawara, *Chem. Lett.*, 391 (1977).
64. A. Ohno, H. Yamamoto, T. Okamoto, S. Oka, and Y. Ohnishi *Bull. Chem. Soc. Jap.*, 50, 2385 (1977).
65. K. Nishiyama, N. Baba, J. Oda, and Y. Inouye, *Chem. Commun.*, 101 (1976).
66. K. Kabato, M. Imuta, E. S. Kempner, and H. Ziffer, *J. Org. Chem.*, 43, 2357 (1978).
67. M. Imuta and H. Ziffer, *J. Org. Chem.*, 43, 3530 (1978).
68. J. Kopilov, E. Kariv, and L. L. Miller, *J. Am. Chem. Soc.*, 99, 3450 (1977).
69. E. Kariv, H. A. Terni, and E. Gileadi, *J. Electrochem. Soc.*, 120, 639 (1973).
70. E. Kariv, H. A. Terni, and E. Gileadi, *Electrochim. Acta*, 18, 433 (1973).
71. J. Kopilov, S. Shatzmiller, and E. Kariv, *Electrochim. Acta*, 21, 535 (1976).

RECENT SIGMATROPIC ROUTES TO INDOLES

Reported by William F. Burgoyne

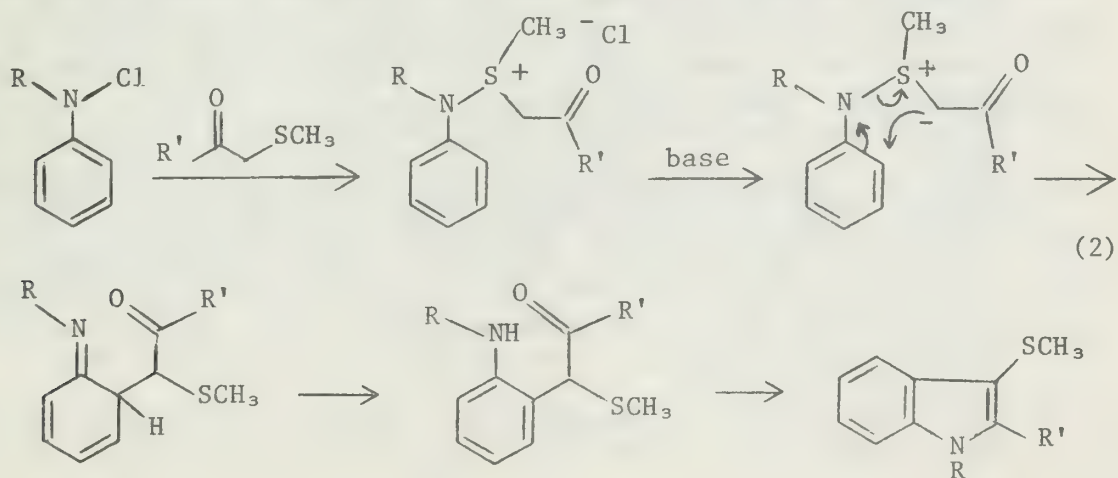
October 5, 1978

The indole nucleus is present in a number of naturally occurring, nitrogen-base compounds, many of which are alkaloids.^{1a} The biological and therapeutic importance of many of these compounds has focussed attention on their efficient preparation.^{1a} Many methods have been developed and employed for stratetic placement of the indole nucleus in various compounds.¹ Perhaps the most well-known of these procedures is the classical Fischer Indole synthesis.² This synthesis (Eq. 1) has as its key step an acid catalyzed [3,3] sigmatropic rearrangement of an aryl hydrazone 1. Its widespread use has resulted from its versatility,³



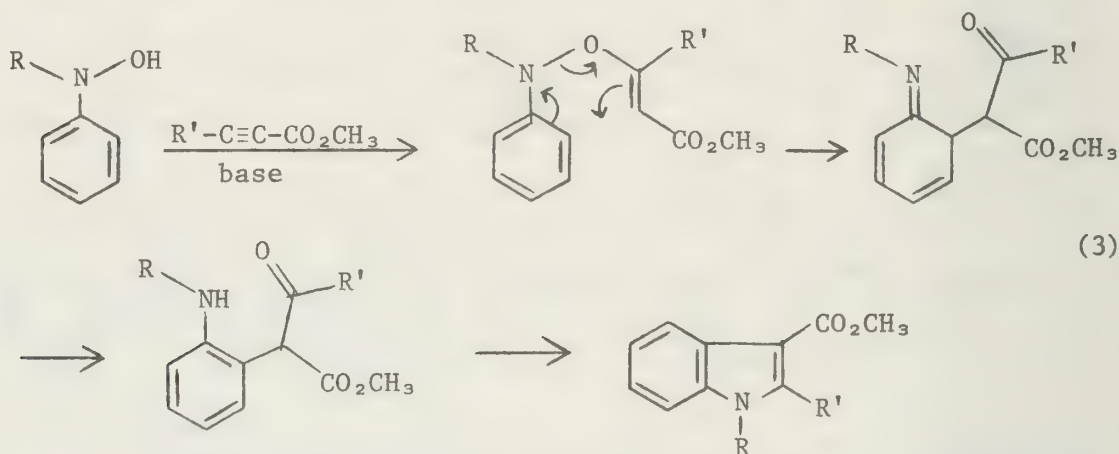
especially when coupled with the Japp-Klingemann reaction.⁴ Since the first report of the rearrangement in 1883,^{2a} numerous studies have been conducted to determine its mechanism,^{1a,3} to achieve optimum yields under catalytic conditions, and to control the product distribution resulting from the cyclization of phenylhydrazones of unsymmetrical ketones.⁵⁻⁷

Recently, two new methods for the regiocontrolled preparation of indoles have been presented. As a result of studies dealing with the formation and chemistry of nitrenium ions,⁸ Gassman has provided a method which allows the specific ortho-alkylation of anilines⁹ and phenols.¹⁰ The rearrangement involves a [2,3] sigmatropic rearrangement^{11a} of an ylide, modeled after the classical Sommelet-Hauser rearrangement.¹² Its utility as an indole synthetic procedure (Eq. 2) is accomplished through



the addition of a β -keto sulfide to an N-chloro aniline. With rearrangement of the ylide and rearomatization, ring closure can occur, providing a synthetic route to the indole nucleus.¹³

A method involving a [3,3] sigmatropic rearrangement is currently being investigated independently by Coates¹⁴ and Sheradsky.¹⁵ This method involves a 1-aza-1'-oxa-[3,3] sigmatropic rearrangement of O-vinyl-N-aryl hydroxylamines to specifically, ortho-alkylated anilines. Synthesis of the O-vinyl N-aryl hydroxylamines is performed by addition of a vinyl equivalent to an N-aryl hydroxylamine. Michael addition of an acetylene carboxylate to an N-aryl hydroxyl amine with subsequent rearrangement illustrates one case (Eq. 3). Other examples of this type of rearrangement have been reported¹⁶ along with the rearrangements of N-vinyl-O-aryl hydroxylamines which can result in the formation of benzofurans.^{15,17}



These new methods provide synthetically useful additions to presently known methods for indole preparation. These rearrangements not only provide routes to specifically substituted indoles but also provide an important access to ortho-alkylated, aromatic systems.

BIBLIOGRAPHY

- (a) W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds", Vol. 8, Interscience Publishers, Inc., New York, 1954; (b) R. J. Sandburg, "The Chemistry of Indoles", Academic Press, New York, 1970, Chapter 3; (c) R. K. Brown, "Indoles", Part I, W. J. Houlihan, Ed., Wiley-Interscience, New York, 1972, Chapter 2.
- (a) E. Fischer and F. Jourdan, Chem. Ber., 16, 2241 (1883); (b) E. Fishcher and O. Hess, *ibid.*, 17, 559 (1884); (c) E. Fischer, Justus Liebigs Ann. Chem., 236, 126 (1886).
- For reviews, see B. Robinson, Chem. Rev., 63, 373 (1963); 69, 227 (1969).
- (a) F. R. Japp and F. Klingemann, Chem. Ber., 20, 2942, 3284, 3398 (1887); (b) R. R. Phillips, Org. React., 10, 143 (1959).
- G. Plancher and A. Bonavia, Gazz. Chim. Ital., 32, 418 (1902).
- (a) K. H. Pausacker, J. Chem. Soc., 621 (1950); (b) N. P. Buu-Hoi, P. Jacquignon, and D. Perin-Roussel, Bull. Soc., Chim. Fr., 2849 (1965); (c) A. H. Kelly, D. H. McLeod, and J. Parrick, Can. J. Chem., 43, 296 (1965).
- (a) R. E. Lyle and L. Skarlos, Chem. Commun., 644 (1966); (b) H. Illy and L. Funderburk, J. Org. Chem., 33, 4283 (1968); (c) M. H. Palmer

- and P. S. McIntyre, J. Chem. Soc. B, 446 (1969); (d) F. M. Miller and W. N. Schinske, J. Org. Chem., 43, 3384 (1978) and references cited therein; (e) F. M. Miller and R. A. Lohr, Jr., ibid., 43, 3388 (1978).
8. (a) P. G. Gassman, Acc. Chem. Res., 3, 26 (1970); (b) P. G. Gassman and G. Hartman, J. Am. Chem. Soc., 95, 449 (1973) and references cited therein.
9. (a) P. G. Gassman, G. Gruetzmacher, and R. H. Smith, Tetrahedron Lett., 497 (1972); (b) C. R. Johnson, C. C. Bacon, and W. D. Kingbury, ibid., 501 (1972); (c) P. G. Gassman and G. A. Campbell, J. Am. Chem. Soc., 94, 3891 (1972); (d) P. G. Gassman and G. D. Gruetzmacher, ibid., 96, 5484 (1974); (e) P. G. Gassman and R. L. Parton, Tetrahedron Lett., 2055 (1977).
10. P. G. Gassman and D. R. Amick, Tetrahedron Lett., 889, 3463 (1974); Syn. Comm., 5, 325 (1975).
11. (a) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry", Ed., Weinheim, Bergst. Verlag Chemie, Academic Press, New York, 1970; (b) J. B. Hendrickson, Angew. Chem. Int. Ed. Engl., 13, 47 (1974).
12. (a) M. Sommelet, C. R. Acad. Sci., 205, 56 (1937); (b) G. C. Jones and C. R. Hauser, J. Org. Chem., 27, 3572 (1962); (c) G. C. Jones, W. Q. Beard, and C. R. Hauser, ibid., 28, 199 (1963).
13. (a) P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., J. Am. Chem. Soc., 96, 5495 (1974); (b) P. G. Gassman, D. P. Gilbert, and S. M. Cole, J. Org. Chem., 42, 3233 (1977); (c) P. G. Gassman and R. J. Balchunis, ibid., 42, 3236 (1977); (d) P. G. Gassman and W. N. Schenk, ibid., 42, 3240 (1977); (e) P. G. Gassman and T. J. van Bergen, J. Am. Chem. Soc., 96, 5508 (1974); (f) P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, ibid., 96, 5512 (1974); (g) P. G. Gassman, B. W. Cue, Jr., and T. Y. Luh, J. Org. Chem., 42, 1344 (1977); (h) P. G. Gassman and R. L. Parton, J. C. S. Chem. Commun., 694 (1977).
14. (a) R. M. Coates and I. Md. Said, J. Am. Chem. Soc., 99, 2355 (1977); (b) R. M. Coates and C. Hutchins, unpublished results; (c) R. M. Coates and W. F. Burgoyne, unpublished results.
15. (a) T. Sheradsky, E. Nov, S. Segal, and A. Frank, J. C. S. Perkin I, 16, 1827 (1977).
16. (a) C. H. Hassall and A. E. Lippman, J. Chem. Soc., 1059 (1953); (b) R. N. Pratt, D. P. Stokes, G. A. Taylor, and P. C. Brookes, J. Chem. Soc. (C), 2086 (1968); (c) B. S. Thyagarajan, J. B. Hillard, K. V. Reddy, and K. C. Majumdar, Tetrahedron Lett., 1999 (1974); (d) J. Hillard, K. V. Reddy, K. C. Majumdar, and B. S. Thyagarajan, J. Heterocycl. Chem., 11, 369 (1974); (e) T. Kato, K. Tabei, and E. Kawashima, Chem. and Pharm. Bull., 24, 1544 (1976) and ref. cited therein.
17. (a) T. Sheradsky, Tetrahedron Lett., 5226 (1966); (b) D. Kaminsky, J. Shavel, Jr., and R. I. Meltzer, ibid., 859 (1967); (c) A. Mooradian, ibid., 407 (1967); (d) A. Mooradian and P. E. Dupont, ibid., 2867 (1967); (e) M. E. Carter and B. Robinson, Chem. and Ind., 304 (1974); (f) T. Sheradsky and G. Salemnick, J. Org. Chem., 1061 (1971).

MULTIPARAMETER CORRELATIONS FOR DESCRIPTIONS OF SOLVENT EFFECTS

Reported by Matt White

October 9, 1978

A general theory which quantitatively describes solvent effects on chemical and physical phenomena has not been developed to date.¹⁻³ However, reliable predictions have been made using empirical relationships of the form given in Eq. 1.^{1,2} In this equation, X is the observed

$$X - X_0 = aP + b \quad (1)$$

chemical or physical property relative to the reference, X_0 , P is the empirical parameter suggested to describe the solvent's major influence on X, and a and b are values obtained from the linear regression analysis. Grunwald and Winstein's Y,⁴ Gielen and Nasielski's x,⁵ Berson's Ω ,⁶ Lassau and Junger's $\log k(\text{Pr}_3\text{N} + \text{MeI})_{20^\circ}$,⁷ Brownstein's S,⁸ and Winstein's $\log k_1$,^{7,5,9} are empirical solvent scales obtained for cases in which X is a chemical process. Situations in which X represents spectroscopic behavior include Dimroth's E_T ,¹⁰ Brooker's X_R ,¹¹ Zelinskii's universal solvent scale,¹² Kosower's Z,¹³ Walther's E_K ,¹⁴ Taft's P,¹⁵ Davis's A,¹⁶ Koppel and Paju's β ,^{17,18} Allerhand and Schleyer's G,¹⁹ Dubois's ϕ ,²⁰ and Knauer and Napier's A_N .²¹ Other solvent scales include Hildebrand's δ ,²² Rudakov's ω ,²³ and Kreshkov's E_S .²⁴ Many of the empirical polarity parameters have been found to be linearly related to each other over a narrow range of selected solvents.²⁵ The one-parameter empirical solvent scales are valid if one solvent-solute interaction or linearly related multiple solvent-solute interactions are dominant in determining X. However, some empirical parameters have been shown not to fit the proposed relationships²⁶⁻²⁸ and recently attention has focused on multiparameter approaches.

Multiparameter approaches will accommodate solvent-solute interactions which act independently of one another if each interaction is describable as a linear effect. The multiparameter approach can be represented by Eq. 2, where X and X_0 have their previous significance, A, B, and C are

$$X - X_0 = aA + bB + cC + \dots \quad (2)$$

solvent parameters representing particular solvent-solute interactions, and a, b, and c are values from the linear regression analysis measuring the sensitivity of X to the changes in solvent. The parameters in this analysis are usually related to specific interactions in contrast to the one-parameter system.

One multiparameter approach formulates specific solvent-solute interactions in terms of separate electrophilic and nucleophilic solvating effects of the solvent. Fawcett and Krygowski have used Dimroth's E_T values to describe the solvent's electrophilic solvating power and Gutmann's donor number, DN, to describe the solvent's nucleophilic solvating power with success.^{29,30} However, E_T values have been found to be sensitive to polarity and polarizability effects and as the electrostatic dependence of X on these interactions decreases, the correlations with E_T and DN decrease.^{29,30} Kosower's Z and Gutmann's acceptor number, A_N , have been proposed to describe the electrophilic properties of the solvent, while Koppel and Paju's β has been proposed to describe the nucleophilic properties.²⁹ These parameters appear to offer little improvement over correlations with E_T and DN.^{28,29,31,32}

A different approach has been proposed by Koppel and Palm in which solvent electrophilic and nucleophilic solvating power and solvent polarity and polarizability are taken into account.²⁴ Koppel and Palm applied this model to rate and spectroscopic data with moderate success, although a major problem is the choices in model processes for their empirical parameters.^{3,18,33,34}

Kamlet and Taft recently have derived a new set of empirical solvent parameters from shifts in the uv absorption of a number of substrates.³⁵ The obtained parameter π^* correlates the solvent's polarity and polarizability effect.³⁵ In this model the solvent effect of hydrogen bonding is dealt with separate terms also obtained spectroscopically. The term α correlates the solvent's power to donate a proton in a hydrogen bond with solute,³⁵ and β correlates the solvent's power to accept a proton in a hydrogen bond with solute.³⁷ Kamlet and Taft parameters to date have been applied to only a few systems.³⁸⁻⁴¹

In the near future it appears the development of approaches for modeling solvent effects will involve multiparametric aspects. Investigations of empirical parameters that describe a variety of data may now be fruitful. Interpretations of the regression coefficients should provide a greater understanding of the effect of molecular environment on physical and chemical processes.

BIBLIOGRAPHY

1. E. S. Amiss and J. F. Hinton, "Solvent Effects on Chemical Phenomena", Academic Press, New York, 1973.
2. J. Shorter, "Correlation Analysis in Organic Chemistry: an Introduction to Linear Free Energy Relationships", Clarendon Press, Oxford, 1973, pp. 74-78.
3. I. A. Koppel and V. A. Palm, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Plenum Press, New York, 1972, chapter 5.
4. E. Grunwald and S. Winstein, J. Am. Chem. Soc., 70, 846 (1948).
5. M. Gielen and J. Nasielski, J. Org. Met. Chem., I, 173 (1963).
6. J. A. Berson, Z. Hamlet, and W. A. Mueller, J. Am. Chem. Soc., 84, 297 (1962).
7. C. Lassau and J. C. Jungers, Bull. Soc. Chim. France, 2678 (1968).
8. S. Brownstein, Can. J. Chem., 38, 1590 (1960).
9. S. G. Smith, A. H. Fainberg, and S. Winstein, J. Am. Chem. Soc., 83, 618 (1961).
10. K. Dimroth, C. Reichardt, T. Seipman, and F. Bohmann, Justus Liebigs Ann. Chem., 661, 1 (1963).
11. L. G. S. Brooker, A. C. Craig, D. W. Heseltine, P. W. Jenkins, and L. L. Lincoln, J. Am. Chem. Soc., 87, 2433 (1965).
12. I. A. Zhmyreva, V. V. Zelinsky, V. P. Kolobkov, and N. D. Krasnitskaya, Dokl. Akad. Nauk., S.S.R., 129, 1089 (1959).
13. E. M. Kosower, J. Am. Chem. Soc., 80, 3253 (1958).
14. D. Walther, J. Prakt. Chem., 316, 604 (1974).
15. R. W. Taft, G. B. Klingsmith, E. Price, and I. R. Fox, Symposium on Linear Free Energy Correlations Preprints of Papers, p. 265 (1964).
16. K. M. C. Davis, J. Chem. Soc. (B), 1128 (1967).
17. I. A. Koppel and A. I. Paju, Org. Reactivity, 11, 121 (1974).
18. A. G. Burden, G. Collier, and J. Shorter, J. Chim. Soc. Perkin II, 1627 (1976).

19. A. Allerhand and P. v. R. Schleyer, J. Am. Chem. Soc., 85, 374 (1963).
20. J. E. Dubois and A. Bienvenue, J. Chem. Phys., 65, 1259 (1968).
21. B. R. Knauer and J. J. Napier, J. Am. Chem. Soc., 98, 4395 (1976).
22. J. H. Hildebrand's and R. L. Scott, "Regular Solutions", Prentice-Hall, Edgewood Cliffs, N.J., 1962, pp. 88-103.
23. E. S. Rudakov, Reakts. Sposobnost. Org. Soedin, 2, 267 (1965).
24. A. P. Kreshkov, L. N. Bykova, and N. A. Kazaryan, "Acid Base Titration in Non-Aqueous Solutions", Khimiya, Moscow, 1962.
25. J. L. Abboud, M. J. Kamlet, and R. W. Taft, J. Am. Chem. Soc., 99, 8325 (1977).
26. F. W. Fowler, A. R. Katritsky, and R. J. Rutherford, J. Chem. Soc. (B), 460 (1971).
27. F. Figueras, J. Am. Chem. Soc., 93, 3255 (1971).
28. O. W. Kolling, Anal. Chem., 50, 212 (1978).
29. W. R. Fawcett and T. M. Krygowski, Can. J. Chem., 54, 3283 (1976).
30. (a) T. M. Krygowski and W. R. Fawcett, J. Am. Chem. Soc., 97, 2143 (1975); (b) W. R. Fawcett and T. M. Krygowski, Aust. J. Chem., 28, 2115 (1975).
31. V. Gutmann, Chem. Tech., 7, 255 (1977).
32. D. N. Waters and Z. Kantarci, J. Raman Sp., 6, 251 (1977).
33. A. G. Burden, N. B. Chapman, H. F. Duggua, and J. Shorter, J. Chem. Soc., Perkin II, 296 (1978).
34. (a) N. B. Chapman, M. R. J. Dack, D. J. Newman, J. Shorter, and R. Wilkerson, J. Chem. Soc. Perkin II, 962 (1974); (b) N. B. Chapman, D. J. Newman, J. Shorter, and H. M. Wall, J. Chem. Soc. Perkin II, 847 (1976).
35. M. J. Kamlet, J. L. Abboud, and R. W. Taft, J. Am. Chem. Soc., 99, 6027 (1977).
36. R. W. Taft and M. J. Kamlet, J. Am. Chem. Soc., 98, 2886 (1976).
37. M. J. Kamlet and R. W. Taft, J. Am. Chem. Soc., 98, 377 (1976).
38. R. J. Highet and F. E. Chou, J. Am. Chem. Soc., 99, 3538 (1977).
39. M. E. Jones, R. W. Taft, and M. J. Kamlet, J. Am. Chem. Soc., 99, 8452 (1977).
40. P. Beak and J. B. Covington, J. Am. Chem. Soc., 100, 3961 (1978).
41. T. Yokoyama, R. W. Taft, and M. J. Kamlet, J. Am. Chem. Soc., 98, 3233 (1976).
42. References dealing with multiparameter models to describe solvent effects on solvolysis reactions: (a) F. L. Schadt, T. W. Bentley, and Paul v. R. Schleyer, J. Am. Chem. Soc., 98, 7667 (1978); (b) S. Winstein, Arnold H. Fainberg, and E. Grunwald, J. Am. Chem. Soc., 79, 4146 (1968); (c) C. G. Swain, D. C. Dittmer, and L. E. Kaiser, J. Am. Chem. Soc., 77, 3737 (1955).

THEORETICAL MODELS FOR THE STABILIZATION OF
CARBANIONS BY ADJACENT SULFUR

Reported by Paul Sherwin

October 12, 1978

Introduction. The propensity of sulfur to stabilize an adjacent formal carbanion is well known and routinely exploited in organic synthesis,¹ yet the mechanism by which sulfur effects such stabilization remains a subject of controversy. As a result of both theoretical and experimental work in this area, several models have been proposed to explain carbanion stabilization by sulfur. This abstract will summarize the important experimental and theoretical work related to these models, judge each on its ability to rationalize certain experimental results, and finally, mention possible future work.

The Nature of α -Sulfo Carbanions. The superiority of sulfur over oxygen in acidifying α C-H bonds is qualitatively exemplified by the observation that anisole undergoes exclusive ring metallation on treatment with strong base, whereas side chain metallation is the thermodynamically preferred mode with thioanisole.² The acidifying ability of sulfur is enhanced by an increase of sulfur oxidation state; thus, the observed order of acidifying ability of sulfur functional groups is: sulfonyl (RSO_2) > sulfonium (R_2S^+) > sulfinyl (RSO) > sulfenyl (RS).³

Studies of the base catalyzed deuterium/hydrogen exchange rates of various substituted carbon acids,⁴ along with equilibrium pKa measurements⁵ (Table 1), have served to quantitatively assess the acidifying effects of sulfur, although the validity of the kinetic acidity as a measure of carbanion stability is open to question.^{5b}

The results of recent ab initio molecular orbital studies⁶ parallel the experimental results in predicting a greater carbanion stabilization in the gas phase by α sulfur than by α oxygen.

Table 1. Representative Thermodynamic Acidities of Some Heteroatom Substituted Carbon Acids

<u>Compound</u>	<u>pKa</u>	<u>$\Delta\Delta\text{pKa}$</u>	<u>Reference</u>
$\text{PhOCH}_2\text{COPh}$ (1)	21.1	-1.2	5a
$\text{PhSCH}_2\text{COPh}$ (2)	17.1	3.7	5a
$\text{PhSeCH}_2\text{COPh}$ (3)	18.6	2.9	5a
PhSO_2COPh (4)	11.4	6.2	5e
$(\text{nPhS})_2\text{CH}$ (5)	31.3	—	5e

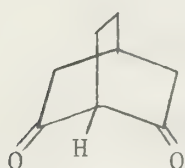
The superiority of sulfur in stabilizing carbanions cannot be attributed solely to inductive effects, since oxygen ($\chi = 3.44$)⁷ is more electronegative, and selenium ($\chi = 2.55$)⁷ is only slightly less electronegative than sulfur ($\chi = 2.58$).⁷ A mesomeric effect is the classical complementary explanation; the results of several experimental investigations appear to be quite consistent with such a hypothesis. Hammett correlations⁸ of a series of substituted benzoic acids, phenols, and anilinium ions have indicated electron pair accepting abilities for the methylsulfinyl, methylsulfonyl, and dimethylsulfonio groups to be in the order $\text{MeSO}_2 > \text{MeSO} > \text{Me}_2\text{S}^+$, as judged by $\Delta\sigma$ values. The $\Delta\sigma$ values, obtained by taking the difference between the σ_{para} and σ_{meta} values,

were taken as a reasonable measure of the substituents' conjugative ability. The methyl sulphenyl group apparently did not act as a strong electron pair acceptor, and this was suggested to mean that the conjugation was too small to be important unless a very large charge density was adjacent to sulfur.

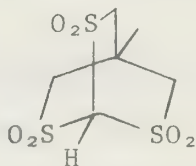
More directly pertinent to the topic of α sulfo carbanion stability is the equilibrium pKa work of Bordwell.⁵ The acidifying effects of α sulfo substituents in model carbon acids were compared to the Δ pKa values for a model in which only an inductive effect would operate. The Δ pKa of the model was calculated from the Taft equation ($\sigma_{1\rho} = \Delta$ pKa). The difference between the estimate for the model and the observed values, $\Delta\Delta$ pKa, was taken as a measure of the conjugative interactions of the substituents with the α carbanion. While the specific values of $\Delta\Delta$ pKa were dependent on the structure of the carbon acid, they were in all cases consistent with conjugative interactions increasing in the order $RO \ll RS < RSO < RSO_2$ (representative $\Delta\Delta$ pKa values are shown in Table 1).

In contrast to the above results, Streitwieser has concluded there is a lack of strong conjugation between the sulfur atoms and the carbanionic lone pair in the 1,3 dithianyl carbanion, based on his measurements of the pKa values of a series of 2-substituted 1,3 dithianes in cyclohexylamine.^{9a}

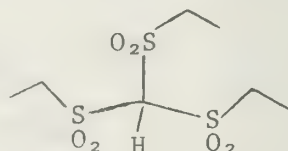
Several experimental results^{5e,11} have led to the conclusion that carbanion stabilization by adjacent sulfur is not sterically restricted; thus, steric inhibition to resonance, of the sort which makes 2,6-diketobicyclo[2.2.2]octane (6) markedly less acidic than acetylacetone,¹⁰ apparently is not operative in S,S,S hexaoxo-4-methyl-2,6,7-trithiabicyclo[2.2.2]octane (7) which is thermodynamically about as acidic as its acyclic analog, S,S,S hexaoxo-triethyltrithioorthoformate (8).¹¹



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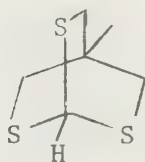


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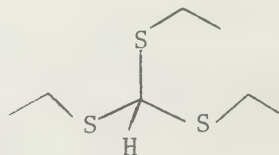


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Although the ca. 10^3 fold greater kinetic acidity of 9 compared to 10 has been interpreted^{4b,h,6c} as indicative of a special stereoelectronic



9



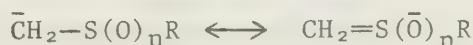
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effect arising from the rigid conformation of 9, Bordwell has argued that in this case, the difference must be due to solvation or steric effects since 9 and the acyclic analog, 5, have closely similar pKa values.^{5e}

The experimental work establishes the acidifying effect of sulfur on an α carbon-hydrogen bond in comparison to α seleno and oxo substituents, and in the series RSO_2 , R_2S^+ , RSO , and RS . There appears to be a conjugative electron pair accepting ability of sulfur, and a lack of steric inhibition to carbanion stabilization. A reasonable theoretical model should explain these effects. Three models have been proposed to date: 1) $d_\pi\text{-p}_\pi$ bonding; 2) polarization; and 3) hyperconjugation.

The theoretical results which have been cited are probably best viewed as guidelines in model development, since they apply strictly only to the gas phase, and because of their approximate nature. Experimental data are therefore the only reliable criteria by which to gauge a model.

The $d_\pi\text{-p}_\pi$ Bonding Model. The earliest¹² and most frequently^{4a-g, 11-13} invoked model for α carbanion stabilization by sulfur postulates $d_\pi\text{-p}_\pi$ overlap of the anionic lone pair with a vacant sulfur 3d orbital leading to a decet of electrons on sulfur. The orbital overlap may be pictorially depicted as:



$$n = 0, 1, 2$$



Early theoretical evaluations of the favorability of $d_\pi\text{-p}_\pi$ bonding were obtained on the basis of calculated $d\text{-p } \pi$ overlap integrals,¹⁵ which provide a measure of the extent of overlap in space of adjacent p and d atomic functions. The assumption that the overlap integral is a reasonable estimate of bond strength¹⁶ then allowed assessment of the favorability of $d_\pi\text{-p}_\pi$ bonding. Evaluation of the overlap integral as a function of some parameter proportional to orbital separation distance led to the conclusion that the sulfur 3d orbitals were probably too diffuse to overlap well with a 2p orbital, and that ligand induced contraction of the d orbitals must be invoked to explain any appreciable d orbital contributions to bonding. In other studies,¹⁷ the efficiency of $d_\pi\text{-p}_\pi$ overlap was estimated by a consideration of the calculated radius of the sulfur 3d orbitals; overlap with a 2p orbital was interpreted as favorable^{17a} or unfavorable,^{17b} depending on the basis set type and the sulfur atomic configuration. Although the conclusions drawn from these studies differ in their assessment of the effectiveness of "isolated" $p\text{-d } \pi$ overlap, it was generally conceded in all the studies that in a molecule the ligands bonded to sulfur could contract the d orbitals, making them more available for bonding. Moreover, the extent of $p_\pi\text{-d}_\pi$ bonding would increase with increasing ligand electronegativity or creation of a formal positive charge on sulfur. Thus, the order of acidifying abilities of α sulfo groups presented above appears to be consistent with the d orbital overlap model.

The validity of using overlap integrals and calculated orbital radii as criteria of bond strengths is questionable; both ignore electrostatic factors and both methods implicitly assume that the energies of

pure, isolated atomic orbitals necessarily reflect the contribution they will make to the molecular wave function. The invalidity of the latter assumption has been discussed recently.¹⁸

A more valid theoretical assessment of the role of sulfur d orbitals in molecular bonding has been made possible by advances in computing which have allowed routine calculations of molecular properties of large molecules. A CNDO molecular orbital study^{4e} of the carbanion derived by deprotonation of 1,3-dithiolane led to the conclusion that the sulfur 3d orbitals contributed ca. 30% to the carbanion stabilization. However, these results may be questionable, since the truncated basis sets employed in the CNDO method give d functions a statistically higher importance compared to extended basis sets. Indeed, a minimal d orbital contribution to carbanion stabilization is indicated by ab initio calculations,^{6,19} which employ basis sets with a greater number of mathematical degrees of freedom than possessed by semi-empirical method basis sets. Thus, calculated proton affinities for the hypothetical $\bar{\text{C}}\text{H}_2\text{-SH}$ anion were only slightly affected by the inclusion of d type functions in the basis set at the ab initio level.⁶ Although in at least one case the lack of d orbital importance was shown to be an artifact of the use of too small 3d function exponents, and correction of the basis set indicated a greater contribution of the 3d orbitals to the molecular wave function, the calculated energies were essentially unchanged, and the conclusion of minimal d orbital importance was maintained.¹⁹ Inclusion of d orbitals in the basis set will naturally lead to some d contribution, but Coulson has suggested that little chemical importance be attached to minor changes associated with their inclusion.²⁰ He therefore suggested that they be viewed as little more than "polarization", or perturbing functions, which serve merely to distort other orbitals.

Nonetheless, interpretation of experimental results in terms of d orbital participation is often done, but is not always unequivocal. In support of the d orbital model, Oae has suggested that the ca. 10^3 fold greater kinetic acidity of 9 over 10 is due to an especially favorable d orbital alignment in 9 enforced by the rigid conformation.^{4b} However, as noted above, Bordwell has shown that such an acidity difference is more consistent with a solvation or steric effect.^{5e} The fact that selenium, whose 4d orbitals should be even higher in energy than sulfur's 3d orbitals, also stabilizes carbanions quite well,²¹ although not as efficiently as sulfur,^{5a,e} may be taken as experimental evidence against d orbital involvement in carbanion stabilization.¹ On the other hand, this latter order is consistent with the expected order of acidification if d orbitals were important in the stabilization.^{5e} Another line of evidence cited in support of the d orbital model is the observation of a marked shift in the IR absorption frequencies of the sulfonyl group upon removal of an α proton, suggestive of delocalization of charge into oxygen via d orbitals.²²

The Polarization Model. An alternative to the d orbital model has been advanced by Streitwieser, who has proposed a highly localized nature for 1,3-dithianyl carbanions on the basis of equilibrium pKa studies^{9a} and ab initio molecular orbital calculations.^{9b} The mechanism of carbanion stabilization was postulated to be "polarization"; i.e., distortion of the charge so as to allow its dispersal over the molecule.



Sulfur has an atomic polarizability of 3.45 \AA^3 as compared with 0.73 for oxygen,²³ and sulfur's more diffuse lone pair can be more easily distorted or "polarized" away from the carbanionic charge. The similarity of this model with Coulson's picture²⁰ of polarization by d orbitals should be noted, although the two concepts differ in origin. Polarization effects have been cited as being important to carbanion stabilization by Wolfe and co-workers^{6a} and by Lehn and Wipff,^{6c} who cited in support of its importance gas phase acidity measurements which suggest that polarization effects are dominant in other systems.²⁴ Bordwell^{5e} has argued that polarizability effects by themselves are insufficient to explain carbanion stabilization by sulfur, since the more polarizable selenium (4.5 \AA^3)²³ does not appear to stabilize carbanions as well as sulfur. On the other hand, if polarization effects were important insofar as they created enough partial positive charge on the heteroatom via a pole induced dipole interaction to contract the d orbitals, making them more available for $d_{\pi}-p_{\pi}$ bonding, then these results would be consistent, but not with polarization as the sole effect. It could also be argued that the longer C-Se bond (2.01 \AA) compared to the C-S bond (1.82 \AA) is responsible, since polarizability effects fall off rapidly with distance. Increasing the effective polarizability of sulfur by bonding to a π system such as a carbonyl group leads to enhanced carbanion stability, as evidenced from the fact that methylthio-2,4,6 tri-isopropyl benzoate is readily deprotonated α to sulfur by methylthiomethyl lithium.²⁵ This has been attributed²⁵ to a formal dipole aiding in the stabilization, which might be expected in the limit of polarization.

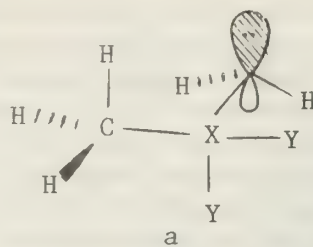
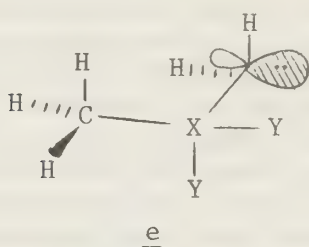
The Hyperconjugation Model. The most recently proposed model of carbanion stabilization by an adjacent sulfur postulates a hyperconjugative charge transfer via overlap of the carbanionic lone pair with an adjacent, low lying S-R antibonding (σ^*) orbital.^{4h,i;6}



The greater carbanion stabilization afforded by adjacent sulfur than by adjacent oxygen is rationalized as follows.^{6b} To a first approximation, the most important orbital interactions with respect to carbanion stabilization are 1) a 4 electron destabilizing interaction between the carbanionic lone pair and the XH σ (bonding) orbital, and 2) a 2 electron stabilizing interaction between the carbon lone pair and the XH σ^* (antibonding) orbital. Treatment of these interactions by perturbation theory led to the conclusion that in the case of $\text{X}=\text{S}$, the 4 electron destabilization would be less severe, due to lesser $n-\sigma$ overlap, and that the 2 electron stabilization would be greater due to a larger $n-\sigma^*$ overlap and a lower lying σ^* orbital,²⁶ than in the case of $\text{X}=\text{O}$.^{6b} Thus, sulfur is more acidifying than oxygen not only because of more stabilization, but also from an effect of less destabilization.

Lehn and Wipff invoked the hyperconjugation model along with polarization to explain the acidifying effects of sulfur as a result of ab initio molecular orbital calculations.^{6c} They calculated the proton affinities for a series of unsubstituted α oxo and α thio carbanions with the carbon lone pair in an equatorial type conformation (11e, 12e, 13e) and an axial type conformation (11a, 12a, 13a). It was calculated that a marked destabilization obtains on conversion of an equatorial type α thio carbanion 13a into an axial type α thio carbanion 13e. This was attributed to

the overall more favorable overlap and the fewer repulsive interactions when the SR σ^* orbital and the carbon lone pair are antiperiplanar than when they are gauche. From the fact that the calculated energy



- 11 X = C, Y = H
12 X = O, Y = lone pair
13 X = S, Y = lone pair

Table 2. Calculated Proton Affinities for Structures 11-13^{6c}

<u>Structure</u>	<u>Proton Affinity (kcal/mole)</u>
<u>11e</u>	557
<u>11a</u>	557
<u>12e</u>	542
<u>12a</u>	547
<u>13e</u>	535
<u>13a</u>	543

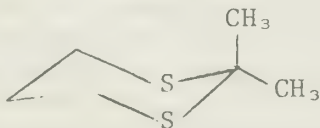
difference of 11a and 13a is ca. 14 kcal/mole, and the calculated energy difference between 13a and 13e is ca. 8 kcal/mole, Lehn and Wipff estimate that the σ^* effect may account for at least half of the total carbanion stabilization. The dramatic influence that this effect would have on carbanion stability is evident from the calculation that a free energy difference of 8 kcal/mole between 2 "frozen" or conformationally rigid carbanions such as 13a and 13e should lead to a ca. 6 unit pKa difference between them at 25°C. Thus, it is not surprising that the hyperconjugation effect has been invoked^{6b,c} to explain the ca. 10^3 fold greater kinetic acidity of 9 over 10, in which case the kinetic acidity difference could translate into as much as 6 pka unit difference in thermodynamic acidity between 9 and 10.^{5e} However, since Bordwell has presented convincing evidence that the kinetic acidity difference in this case is more consistent with a steric or solvation effect, the reality of such a stereoelectronic effect is questionable.^{5e}

Epiotis and co-workers have mentioned that $\bar{\text{C}}\text{H}_2\text{Cl}$, which has no adjacent XR σ^* orbital for hyperconjugative stabilization of the carbanion, is calculated to dissociate into methylene and chloride anion.^{6b} However, any arguments about carbanion stabilization based on reactivities are tenuous, since the reactivity of a species is related to the difference in ground state and transition state energies, and thermodynamic stability pertains to the ground state.

Borden and co-workers have pointed out that consideration of canonical forms for the hyperconjugation of a β thio carbanion might lead one to expect β acidification by sulfur:^{4h}



To test this hypothesis, Borden and co-workers compared the D/H exchange rates of the geminal methyl protons and the C4 and C6 methylene protons in 2,2-dimethyl-1,3-dithiane.^{4h}



The predominant (>94%) exchange at C4 and C6 and the minor exchange (<3%) of the gem methyl protons, led Borden to conclude that the polarizability of sulfur is critical in determining the regiochemistry of proton abstraction in sulfides. This conclusion was supported by ab initio molecular orbital calculations.^{4h}

Borden's experiment might be criticized on steric grounds. Assuming that exchange occurs predominantly with protons situated antiperiplanar to a S-C bond, abstraction of one of the methyl protons would reasonably be expected to involve a higher energy transition state. Therefore, the conclusion of a lack of β acidification in this case may be questionable.

Discussion of the Models. It is clear that while all three models are highly successful in qualitatively rationalizing why sulfur is more acidifying than oxygen, the hyperconjugation and polarization models appear to be lacking in an explanation of why sulfur is more acidifying than selenium. From this standpoint, the d orbital model appears to be preferable.

The difficulty in trying to identify any of the models as the "correct" one is that the theoretical work all pertains strictly to an isolated molecule in the gas phase. Molecules in solution may differ appreciably from those in the gas phase such that a number of effects would be involved.

Solution phase results are difficult to predict using computational techniques due to the difficulty involved in taking solvation effects into consideration in the calculations. Hopefully, the rapidly expanding nature of computer technology will eventually allow theoretical insight into solvation effects.

To unambiguously unravel the factors involved in carbanion stabilization via solution phase chemical experimentation will be a challenge, since carbanion chemistry can be quite sensitive to ion pairing and solvation effects. In addition, intramolecular parameters such as carbon-heteroatom bond lengths, σ and σ^* energies, heteroatom polarizabilities, and heteroatom d orbitals may all be important in α heteroatom carbanion stabilities. If this is the case, it will be difficult if not impossible to factor the stabilization into these components since it is difficult to conceive of a model system in which all the carbanion stabilization models do not predict equivalent results.

One approach which could be taken is suggested by a consideration of the conformational dependence of carbanion stability predicted by the hyperconjugation model. Synthesis of model compounds in which respectively the axial type carbon lone pair and the equatorial type carbon lone pair conformations could be rigidly maintained by geometric constraints might allow gas phase pKa measurements which would provide a direct comparison of the experimental results and the theoretical predictions. However, the results would be useful only in evaluating the hyperconjugation model vs. the polarization and d orbital models. An absence of a conformational dependence of α thio carbanion stability would be consistent with both the d orbital and polarization models, but no further inferences could be drawn regarding these models.

Currently the d orbital model of carbanion stabilization by adjacent sulfur appears to be more consistent with the experimental data presented, since it is the only model of the three which has successfully been employed in the chemical literature to explain the greater acidification by sulfur than by selenium. However, since all of the models are, by necessity, gross oversimplifications of the physical factors at play in nature, a clear and valid judgement must await the outcome of further studies in this area.

BIBLIOGRAPHY

1. For an overview of the uses of sulfur stabilized carbanions in organic synthesis and of the models proposed for carbanion stabilization by sulfur, see E. Block, "Reactions of Organosulfur Compounds", Academic Press, New York, N.Y., 1978, Chapter 2.
2. H. Gilman and F. J. Webb, J. Am. Chem. Soc., 62, 987 (1940).
3. G. Barbarella, A. Gabesi, and A. Fava, Helv. Chim. Acta, 54, 2297 (1971).
4. (a) S. Oae, W. Tagaki, and A. Ohno, J. Am. Chem. Soc., 83, 5036 (1961); (b) S. Oae, W. Tagaki, and A. Ohno, Tetrahedron, 20, 417,427 (1964); (c) S. Oae and Y. Yano, Mech. React. Sulfur Compounds, 4, 167 (1969); (d) A. I. Shatenshtein and A. A. Gvozdeva, Tetrahedron, 25, 2749 (1969); (e) D. L. Coffen, B. D. Grant, and D. L. Williams, Int. J. Sulfur Chem. A, 1, 113 (1971); (f) L. H. Slaugh and E. Bergman, J. Org. Chem., 26, 3158 (1961); (g) W. Drenth and A. Loewenstein, Rec. Trav. Chim., 81, 635 (1962); (h) W. T. Borden, E. R. Davidson, N. R. R. Anderson, A. D. Denniston, and N. D. Epiotis, J. Am. Chem. Soc., 100, 1604 (1978); (i) G. Barbarella, P. Dembech, A. Garbesi, F. Bernardi, A. Bottoni, and A. Fava, J. Am. Chem. Soc., 100, 200 (1978).
5. (a) F. G. Bordwell, M. Van der Puy, and N. R. Vanier, J. Org. Chem., 41, 1883,1885 (1976); (b) F. G. Bordwell, W. S. Matthews, and N. R. Vanier, J. Am. Chem. Soc., 97, 442 (1975); (c) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, J. Am. Chem. Soc., 97, 7006 (1975); (d) F. G. Bordwell, N. R. Vanier, W. S. Matthews, J. B. Hendrickson, and P. L. Skipper, *ibid.*, 97, 7006 (1975); (e) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. Van der Puy, N. R. Vanier, and W. S. Matthews, J. Org. Chem., 42, 326 (1977).
6. (a) F. Bernardi, I. G. Csizmadia, A. Mangini, H. B. Schlegel, M. H. Whangbo, and S. Wolfe, J. Am. Chem. Soc., 97, 2209 (1975); (b) N. D. Epiotis, R. L. Yates, F. Bernardi, and S. Wolfe, *ibid.*, 98, 5435 (1976); (c) J. M. Lehn and G. Wipff, *ibid.*, 98, 7498 (1976).

7. F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", Wiley and Sons, New York, N.Y., 1972, p. 115.
8. (a) F. G. Bordwell and P. J. Boutan, J. Am. Chem. Soc., 78, 854 (1956); (b) F. G. Bordwell and G. D. Cooper, *ibid.*, 74, 1058 (1952); (c) F. G. Bordwell and P. J. Boutan, *ibid.*, 79, 717 (1957); (d) F. G. Bordwell and P. J. Boutan, *ibid.*, 78, 87 (1956).
9. (a) A. Streitwieser, Jr., and S. P. Ewing, J. Am. Chem. Soc., 97, 190 (1975); (b) A. Streitwieser, Jr., and J. E. Williams, *ibid.*, 97, 191 (1975).
10. P. D. Bartlett and G. F. Woods, J. Am. Chem. Soc., 62, 2933 (1940).
11. W. von E. Doering and L. K. Levy, J. Am. Chem. Soc., 77, 509 (1955).
12. (a) E. Rothstein, J. Chem. Soc., 309 (1937); (b) E. Rothstein, J. Chem. Soc., 1550,1558 (1940).
13. (a) G. Cilento, Chem. Rev., 60, 146 (1960); (b) C. C. Price and S. Oae, "Sulfur Bonding", Ronald Press, New York, N.Y., 1962; (c) S. Oae in "The Chemistry of Sulfur Compounds", Vol. 3, N. Kharasch and C. Y. Meyers, eds., Pergamon Press, New York, N.Y.; (d) D. L. Coffen, Rec. Chem. Prog., 30, 275 (1969); (e) K. A. R. Mitchell, Chem. Rev., 69, 157 (1969); (f) D. J. Peterson, Organomet. Chem. Rev. A, 7, 295 (1972); (g) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, N.Y., 1965, pp. 71-84.
14. H. H. Jaffé, J. Phys. Chem., 58, 185 (1954).
15. (a) D. P. Craig and E. A. Magnusson, J. Chem. Soc., 4895 (1956); (b) D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel, and L. E. Sutton, J. Chem. Soc., 332 (1954).
16. R. S. Mullikan, J. Phys. Chem., 56, 295 (1952).
17. (a) D. W. J. Cruickshank, B. C. Webster, and D. F. Mayers, J. Chem. Phys., 40, 3733 (1964); (b) D. P. Craig and T. Thirunamachandran, J. Chem. Phys., 43, 4183 (1965).
18. F. L. Pilar, J. Chem. Ed., 55, 2 (1978).
19. A. Rauk, S. Wolfe, and I. G. Csizmadia, Can. J. Chem., 47, 113 (1969).
20. C. A. Coulson, Nature, 221, 1106 (1969).
21. (a) D. Seebach, Angew. Chem. Int. Ed. Eng., 8, 639 (1969); (b) D. Seebach and N. Peleties, Chem. Ber., 105, 511 (1972); (c) H. J. Reich, J. Org. Chem., 40, 2570 (1975).
22. E. M. Kaiser, L. E. Solter, R. A. Schwarz, R. D. Beard, and C. R. Hauser, J. Am. Chem. Soc., 93, 4237 (1971).
23. J. Thorhallsson, C. Fisk, and S. Fraga, Theor. Chim. Acta, 10, 388 (1968).
24. (a) M. J. S. Dewar and R. C. Dougherty, "The PMO Theory of Organic Chemistry", Plenum Press, New York, N.Y., 1975, pp. 505-515; (b) L. Radom, Aust. J. Chem., 28, 1 (1975).
25. P. Beak and D. B. Reitz, Chem. Rev., 78, 275 (1978).
26. N. D. Epiotis, W. R. Cherry, S. Shaik, R. L. Yates, and F. Bernardi, Top. Curr. Chem., 70 (1977).

NEW APPROACHES TO THE STUDY OF THE MOLECULAR MECHANISM OF STEROID ACTION

Reported by S. G. Senderoff

October 16, 1978

One of the most challenging fields of study for the biological chemist is the field of hormone biochemistry. The past thirty years of intense research has afforded unprecedented progress in our understanding of the molecular basis of cell growth and development, and the application of this knowledge has had profound scientific and cultural influence upon the development of contemporary society. Some of the most significant work in this field was done in the steroid area.

The study of the actions of steroid hormones may be undertaken by utilizing three conceptually different approaches: biological, biochemical, and chemical. The biological or pharmacological approach involves the observation of the endpoints of hormone action, such as growth of a hormone sensitive tissue, in response to the administration of a natural hormone or synthetic analog. The object of the biochemical approach is the isolation and characterization of the macromolecular components involved in the molecular mechanism of steroid action. This approach has led to investigations of the biosynthetic enzymes, serum binding proteins, and intracellular receptor proteins. The newest approach is chemically based. This method is concerned with the interaction of chemically reactive hormone analogs with the macromolecular machinery under investigation in the biochemical scheme. This abstract will review recent applications of the chemical approach to the study of the actions of steroid hormones.

One of the basic facts of molecular endocrinology is that proteins located exclusively in the cells of hormone sensitive tissues are involved in the selective uptake and nuclear retention of hormones.¹ The interaction between the hormone and receptor protein is of a non-covalent nature. The chemical approach of affinity labelling is particularly useful in the study of steroid-protein interactions.

The technique of affinity labelling² involves the synthesis of a hormone analog capable of binding to the receptor of a natural hormone with high affinity. The analog carries a chemically reactive group which may react selectively with an amino acid residue in the receptor binding site producing a covalently bound hormone-receptor complex.

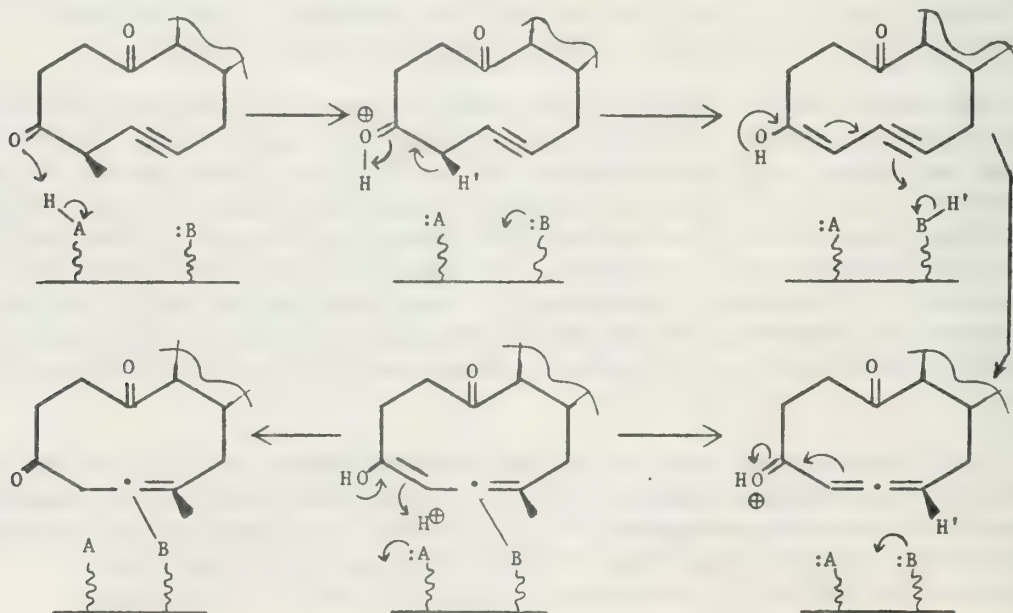
Metabolic events play a major role in the mechanism of steroid action. These events include biosynthesis, conjugation, catabolism, and in the case of the androgens, end organ metabolic activation. The details of the role played by metabolism, and the chemical characterization of the enzymic reactions involved in these metabolic events may be elucidated by the use of suicide inhibitors. A suicide inhibitor^{3,4} carries a group which is converted to a reactive functionality upon binding to the active site by the catalytic activity of the enzyme itself. Covalent bond formation to an active site amino acid residue follows as in the case of the affinity label.

J. C. Warren and his colleagues made extensive use of the affinity labelling technique in their study of the binding site of the enzyme 20 β hydroxy steroid dehydrogenase.^{5a-1} A series of progesterone and cortisone derivatives carrying the electrophilic halo-acetoxy function (steroid—OCOCH₂X) selectively labelled specific amino acid

residues in the active site presumably by an S_N2 mechanism. From these results it was possible to describe the spatial orientations of active site histidine, methionine, and cysteine with respect to the steroid. It was further inferred that a conformational change occurred in the vicinity of the active site upon binding and alkylation, as evidenced by the isolation of 1,3-bis carboxymethyl histidine after acid hydrolysis of the covalent enzyme-affinity label complex. It was also interesting to note that the affinity labelling steroids exhibited long lived bio-activity, unlike the parent steroids.^{6,7}

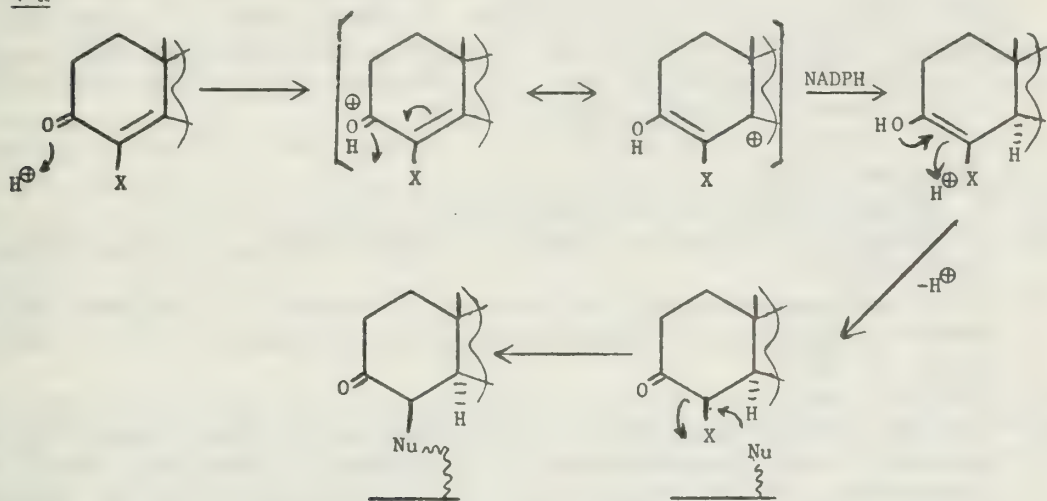
Warren's labelling studies were performed upon homogeneous preparations of 20 β hydroxy steroid dehydrogenase, for the extensive non-specific binding of steroids to hydrophobic portions of macromolecules in heterogeneous preparations would lead to considerable non-specific labelling. This intrinsic drawback of conventional electrophilic affinity labelling may be minimized by devising a process by which the reactivity of the affinity label could be externally controlled. The technique of photoaffinity labelling^{8,9} meets these requirements and has been extensively used by Katzenellenbogen and his colleagues to study the estrogen receptor.^{2,9}

The technique of suicide inhibition has been employed to study the role of the individual steps of steroid biosynthesis in the overall mechanism of steroid action. Robinson and his colleagues have synthesized steroid analogs that served as suicide inhibitors for the enzyme 3-keto steroid $\Delta^5 - \Delta^4$ isomerase.^{10a-f} This enzyme plays a pivotal role in the elaboration of androgens, estrogens, and progestogens from pregnenolone. Robinson's 5-acetylenic 5,10-secosteroids were isomerized by the enzyme to highly electrophilic conjugated allenic species. The keto-allenes rapidly inactivated the enzyme. Although the specific active site amino acid residue bound to the inactivator was not identified, X-ray studies performed upon natural substrate, natural product, suicide substrate and suicide product indicated that the substrates were positioned in the active site by the steroidal C and D rings; interactions with the A ring oxygen helped provide the proper A-B ring conformation for 4 β proton abstraction; and an enzymic conformational change facilitated proton transfer to the 6 β position.

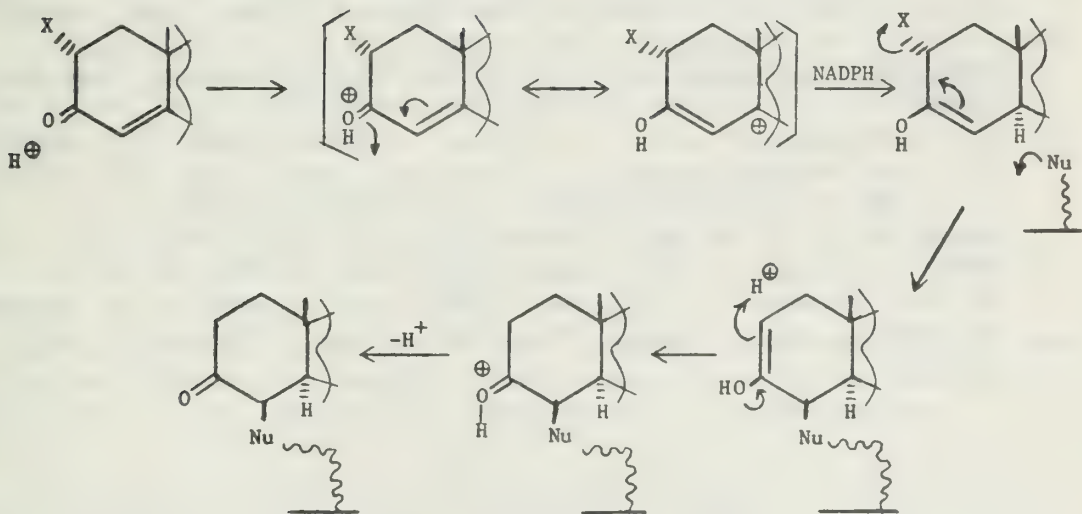


The role and generality of end organ metabolism of testosterone^{11a-c} by the enzyme testosterone 5 α reductase^{12a-g} is currently unclear in the general mechanism of androgen action. Katzenellenbogen and Senderoff in collaboration with J. D. Wilson are employing the techniques of affinity labelling and suicide inhibition to selectively inhibit this enzyme. Three series of ring halogenated testosterone derivatives were synthesized. All of the compounds were inhibitors of 5 α reductase, with K_i values within the same order of magnitude as the K_m value for natural testosterone. Work is now in progress to fully characterize the nature of the inhibition.

4-X



2 α -X



BIBLIOGRAPHY

1. C. D. Turner and J. Bagnara, "General Endocrinology", 6th Ed., Saunders and Company, Philadelphia, 1976.
2. J. A. Katzenellenbogen, "Biochemical Actions of Hormones", Vol. IV, G. Litwack, ed., Academic Press, New York, 1977, p. 1.
3. R. R. Rando, *Science*, 185, 320 (1974).
4. R. H. Abeles and A. L. Maycock, *Accts. Chem. Res.*, 9, 313 (1976).
5. (a) M. Ganguly and J. C. Warren, *J. Biol. Chem.*, 246, 3646 (1971); (b) F. Sweet, F. Arias, and J. C. Warren, *ibid.*, 247, 3424 (1972); (c) C. C. Chin and J. C. Warren, *Biochemistry*, 11, 2720 (1972); (c) F. Sweet and J. C. Warren, *Biochim. Biophys. Acta*, 260, 759 (1972); (e) F. Arias, F. Sweet, and J. C. Warren, *J. Biol. Chem.*, 248, 5641 (1973); (f) R. C. Strickler, F. Sweet, and J. C. Warren, *ibid.*, 250, 7656 (1975); (g) F. Sweet, *Steroids*, 741 (1976); (h) F. Sweet, R. Strickler, and J. C. Warren, *ibid.*, 253, 1385 (1978); (i) F. Sweet, private communication.
6. S. W. Clark, F. Sweet, and J. C. Warren, *Am. J. Obstet. Gynecol.*, 121, 864 (1975).
7. F. Sweet, private communication.
8. A. Singh, E. R. Thorton, and F. H. Westheimer, *J. Biol. Chem.*, 237, 3006 (1962).
9. J. A. Katzenellenbogen, H. Johnson, H. Myers, K. Carlson, and R. Kempton, "Bioorganic Chemistry", Vol. IV, Academic Press, New York, 1978, p. 207.
10. (a) S. K. Malhorta and H. J. Ringold, *J. Am. Chem. Soc.*, 87, 3228 (1965); (b) F. Batzold and C. H. Robinson, *J. Org. Chem.*, 41, 313 (1976); (c) F. Batzold and C. H. Robinson, *J. Am. Chem. Soc.*, 97, 2576 (1975); (d) D. Covey and C. H. Robinson, *ibid.*, 98, 5038 (1976); (e) H. Carrell, J. Glusker, D. Covey, F. Batzold, and C. H. Robinson, *ibid.*, 100, 4282 (1978); (f) F. Batzold, A. Benson, D. Covey, C. H. Robinson, and P. Talalay, *Adv. Enz. Reg.*, 14, 243 (1976).
11. (a) J. D. Wilson and R. J. Gloyana, *Rec. Prog. Hormone Res.*, 26, 309 (1970); (b) J. D. Wilson, *New England J. Med.*, 287, 1284 (1972);
12. (c) W. I. P. Mainwaring, "Mechanism of Action of Androgens", *Monographs on Endocrinology*, Vol. 10, Springer-Verlag, New York, 1977.
12. (a) N. Bruchovsky and J. D. Wilson, *J. Biol. Chem.*, 243, 2012 (1968); (b) D. W. Fredricksen and J. D. Wilson, *ibid.*, 246, 2584 (1971); (c) R. J. Moore and J. D. Wilson, *ibid.*, 247, 958 (1972); (d) R. J. Moore and J. D. Wilson, *Biochemistry*, 13, 450 (1974); (e) W. Voigt, and S. L. Hsia, *J. Biol. Chem.*, 248, 4280 (1973); (f) D. C. Wilton, *Biochem. J.*, 155, 487 (1976); (g) T. Nambara, S. Ikegawa, H. Ishida, and H. Hosoda, *Chem. Pharm. Bull.*, Tokyo, 12, 3415 (1977).

PULSE RADIOLYSIS: A TECHNIQUE FOR THE STUDY OF ORGANIC IONS

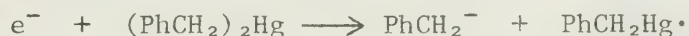
Reported by Raul Oteiza

October 23, 1978

Carbanions¹⁻⁴ and carbocations⁵⁻⁹ are reactive intermediates of broad importance and interest in organic chemistry. Many of the reactions of these ionic species occur so rapidly that special techniques are required for investigations of these ions. The application of the pulse radiolysis technique to the study of carbanions and carbocations in solution¹⁰⁻¹⁵ makes it possible to form and observe these species on a submicrosecond time scale.

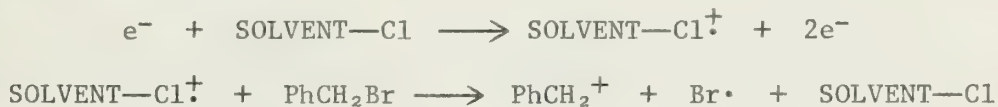
Pulse radiolysis^{16,17} involves a short-lived perturbation of a system from equilibrium by ionizing radiation from an external source, followed by observation of the chemical relaxation of the system. The active external perturbation is a nanosecond to microsecond pulse of electrons of sufficiently high intensity to instantaneously produce a concentration of transient species which may be directly observed.

The formation of carbanions in liquids occurs through the action of solvated electrons as primary reducing species. A dissociative attachment to an appropriate solute occurs, as shown for the ionization of dibenzyl mercury:



If an alkali metal is present in sufficient concentration, the solvated electron may pair with the metal cation to directly give an ion-paired species. An ion-paired species may also be formed by combination of the free carbanion with the metal cation. Once formed, the rate of reaction of these species with various substrates can be determined. This data can be analyzed to reveal the trends in the rates of the protonations of carbanions, the effects of cation pairing on the reactivity of the carbanion, and the relative basicity of hydrocarbon bases.

Carbocations may be formed by the action of the solvent radical-cation formed from a halogenated solvent on an appropriate substrate. An example is benzyl bromide:



The reactivity of the carbocations with various nucleophiles yield data which allow fundamental insights of the reactions of these electrophiles. Charge, steric, and aggregation effects can be readily measured.

The ability to directly observe the reactivity of organic ions promises that pulse radiolysis will become a helpful tool in probing the phenomena of organic reaction mechanisms.

BIBLIOGRAPHY

1. M. Szwarc, "Carbanions, Living Polymers and Electron Transfer Processes", Interscience, New York, 1968.
2. D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, 1965.
3. A. Streitwieser, Jr., D. E. Van Sickle, and W. C. Longworthy, J. Am. Chem. Soc., 84, 244 (1962).
4. R. Waack and M. A. Doran, J. Am. Chem. Soc., 85, 1651 (1963).
5. G. A. Olah and P. v. R. Schleyer, "Carbonium Ions", Vol. I, Interscience, New York, 1968.
6. G. A. Olah and P. v. R. Schleyer, "Carbonium Ions", Vol. II, Interscience, New York, 1968.
7. E. S. Gould, "Mechanism and Structures in Organic Chemistry", Holt, Rinehart, and Winston, New York, 1959, pp. 250-303, 412-610.
8. J. F. Norris, Amer. Chem. J., 25, 117 (1901); J. F. Norris and W. W. Sanders, *ibid.*, 25, 54 (1901).
9. A. Baeyer and V. Villiger, Chem. Ber., 35, 1189, 3013 (1902).
10. B. Bockrath and L. M. Dorfman, J. Am. Chem. Soc., 96, 5708 (1974).
11. R. L. Jones and L. M. Dorfman, *ibid.*, 96, 5715 (1974).
12. B. Bockrath and L. M. Dorfman, *ibid.*, 97, 3307 (1975).
13. R. J. Sujdak, R. L. Jones, and L. M. Dorfman, *ibid.*, 98, 4875 (1976).
14. L. M. Dorfman, R. J. Sujdak, and B. Bockrath, Accts. Chem. Res., 9, 352 (1976).
15. L. M. Dorfman, Y. Wang, H.-Y. Wang, and R. J. Sujdak, Faraday Disc., 93, 149 (1977).
16. M. S. Matheson and L. M. Dorfman, "Pulse Radiolysis", M. I. T. Press, Cambridge, Mass., 1969.
17. J. W. Boag, "Physical Methods in Radiation Chemistry and in Radiobiology", in Actions Chimiques et Biologiques des Radiations, M. Haissinsky, ed., sixième série, Masson and Cie, Paris, 1963, p. 4.

CYCLOADDITIONS OF SILYLOXYDIENES IN ORGANIC SYNTHESIS

Reported by Joseph B. Holtwick

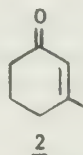
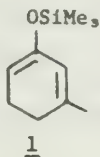
October 26, 1978

Electron-rich silyloxydienes have recently been shown to possess considerable synthetic value in the preparation of polycyclic systems via cycloaddition reactions. As a class, the silyloxydienes exhibit high reactivity and orientational specificity in Diels-Alder reactions with electron-deficient π systems. In addition, these dienes are easily prepared and the resulting cycloadducts are readily convertible to useful functionality. This report will review the preparation and synthetic utility of silyloxydienes.

Generation of Silyloxydienes. Two procedures are commonly employed in the silylation of aldehydes and ketones. The procedure found most satisfactory for aldehydes and symmetrical ketones involves reaction with a tertiary amine, typically triethylamine, and excess trimethylsilyl chloride in dimethyl formamide (DMF) solution.¹ For esters, which demonstrate a propensity for C-silylation, Rathke² has shown that employment of a hindered silylating agent, namely tert-butyl dimethylchlorosilane, with preformed lithium ester enolates results in nearly exclusive formation of the O-silylated derivative. Bozouin³ subsequently discovered that the addition of zinc chloride (ZnCl_2) precluded C-silylation with the triethylamine-trimethylsilyl chloride method.

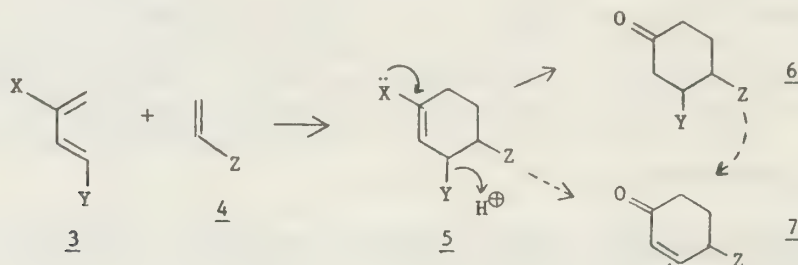
The second commonly employed silylating procedure involves the initial generation of the enolate followed by treatment with trimethylsilyl chloride. Upon investigation of a number of bases, lithium diisopropylamide (LDA) was found to give the most satisfactory results.^{1,4}

Both of these methods have been employed in the synthesis of silyloxydienes in respectable yield. When only one product is possible, the triethylamine-trimethylsilyl chloride method is the method of choice. However, in some cases^{5,6} higher yields of silyloxydienes are obtained by the LDA-trimethylsilyl chloride method. In addition, this latter method provides for the facile preparation of the endocyclic silyloxydiene 1 from ketone 2 even though 2 is well known to enolize to give an exo double bond.⁶



Regiochemistry of Silyloxydienes in Cycloaddition Reactions. Frontier Orbital Theory indicates that the diene HOMO-dienophile LUMO interaction is controlling in cycloadditions of "electron-rich" dienes with "electron-poor" dienophiles. Furthermore, the 1,2-regioisomer is favored with 1-substituted butadienes while the 1,4-regioisomer is favored with 2-substituted butadienes.^{7,8} Only in those cases in which both diene and dienophile are electron-rich will this regiochemistry be predicted as reversed and the 1,3-regioisomer favored. Experimental evidence is in general agreement with theory.⁹⁻¹¹

In general, the construction of useful cycloadducts by the $4\pi + 2\pi$ cycloaddition is somewhat limited due to a lack in variation in terms of functionality and oxidation level of the 4π component.⁹ In an analysis of this situation, Danishefsky¹² proposed the following generalized transformation as desirable for a number of synthetic objectives:



The nature of substituents X and Y should enhance 4π reactivity and orientational specificity when reacted with a dienophile where Z is an electron withdrawing group. The substituent X should also allow for the facile transformation to other useful functionality. In addition, the functional group Y should be a leaving group or convertible to another utilizable function. The structural requirements set forth above are met by 1,3-silyloxybutadiene, which generated the investigation into the synthetic utility of silyloxydienes.

The electron-rich silyloxydienes demonstrate a high order of orientational specificity in reactions with electron-deficient dienophiles. The reaction of 2-trimethylsilyloxy-1,3-butadiene (8) with several dienophiles (below) as summarized in Table 1 is illustrative. In those cases in which positional isomers are possible (*i.e.*, 10a, 10b), the 1,4-isomer was exclusively isolated.⁵

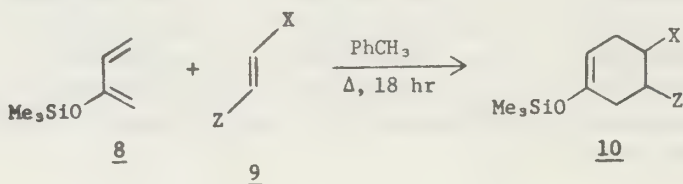


Table 1. Diels-Alder Reactions of 2-Silyloxybutadienes

Compound	X	Z	Yield* of <u>10</u> (%)
a	COCH ₃	H	60
b	CO ₂ CH ₃	H	35
c	CO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	77
d	CO ₂ CH ₃	CO ₂ CH ₃	71

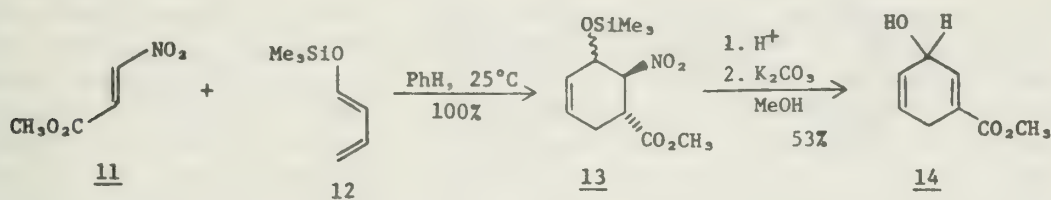
* yield of isolated pure cycloadducts without optimization

These results are in contrast with those obtained in the reactions of 2-alkoxy-1,3-butadienes, which normally yield a mixture of the 1,3-regioisomer and 1,4-regioisomer, the latter of which predominates.^{9,13}

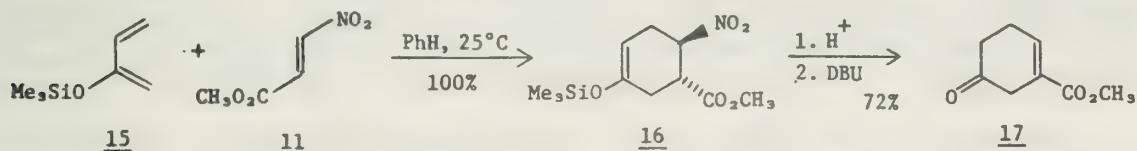
In all cases to date, silyloxydienes with orientationally reinforcing substituents afford the concurrent 1,2-1,4-regioisomers as the exclusive

Diels-Alder product. For example, the reaction of trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene with methacrolein yields only the 4,4-disubstituted cyclohexanone upon acid hydrolysis in 72% yield.¹⁴

Only one case in which a 1-substituted trimethylsilyloxydiene has undergone cycloaddition with an unsymmetrical electron-deficient dienophile has been reported.¹⁵ This exploratory investigation sought to find a dienophile capable of providing a regiochemical pattern in opposition to the 1,2-adducts generally available from Diels-Alder reactions of acetylenic dienophiles with nucleophilic dienes. A solution to this problem was afforded upon consideration of the readily available trans-methyl β-nitroacrylate (11). Cycloaddition of 11 with trans-1-trimethylsilyloxy-1,3-butadiene (12) yielded a quantitative mixture of the stereoisomeric adducts 13.

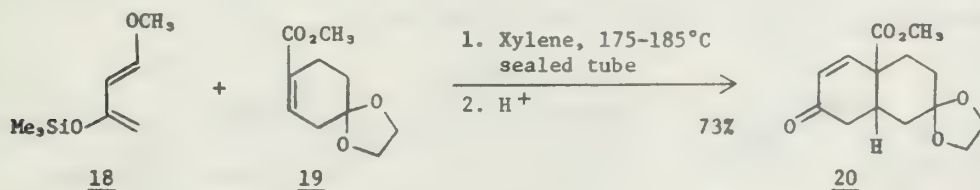


Diels-Alder cycloaddition of 2-trimethylsilyloxy-1,3-butadiene (15) with 11 yields only the cycloadduct 16.



In view of the adherence of diene 15 to regiochemical predictions with regard to reaction with electron-deficient dienophiles,⁵ two conclusions can be drawn. First, the nitro group exercises complete regiochemical control in the Diels-Alder reaction. Secondly, 1-silyloxydienes react in 1,2-fashion with electron-deficient dienophiles.

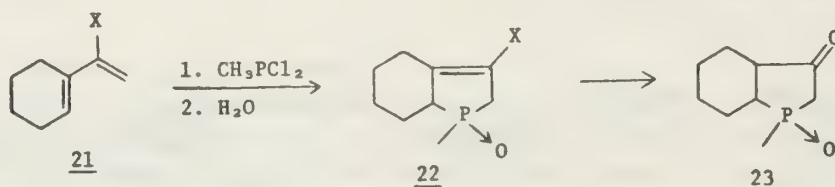
Hydrolysis of Cycloadducts. Silyl enol ethers, although still subject to acid hydrolysis like alkyl enol ethers, may be hydrolyzed under effectively neutral conditions. For example, the cycloadduct generated in the reaction of 2-trimethylsilyloxy-1,3-butadiene with dimethylfumarate was converted to the keto-derivative in >95% yield upon treatment with methanol (25°C; 24hr) or $\text{KF} \cdot 2\text{H}_2\text{O}$ (THF; 25°C; 5hr).⁵ Further illustrative of the mild conditions necessary for conversion to ketones is the hydrolysis yielding cycloadduct 20.



Treatment of the reaction mixture with 3:1 THF:0.005N aqueous HCl at -5 to 0°C for 10 min allowed for maintenance of the ketal while the β -methoxysilyl enol ether was transformed to the desired enone.¹⁶

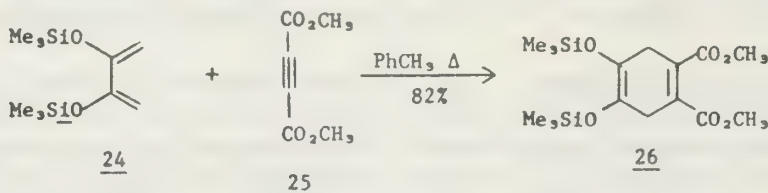
Use of Silyloxydienes in Synthesis. Silyloxydienes have been employed in numerous synthetic schemes.¹⁷

In 1968, Quin¹⁸ reported the preparation of the first known mono-cyclic keto-derivative of the phospholane family via the McCormack reaction.¹ Subsequently, extension to include the synthesis of a bicyclic 3-phospholanone was undertaken. Thus, 1-(α -halovinyl)cyclohexenes (21) were condensed with methylphosphonous dichloride.

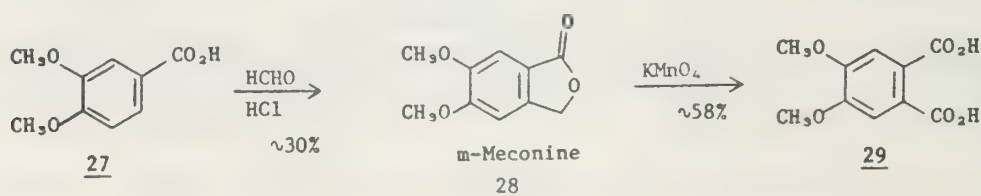


Treatment of 22 with sodium methoxide followed by acid hydrolysis might lead to the desired bicyclic 3-phospholanone in ~8% overall yield based on model compounds. An improved route to 23²⁰ begins with the conversion of 1-acetylcyclohexene to its corresponding silyloxydiene. Subsequent treatment with methylphosphonous dichloride followed by hydrolysis with water afforded the 3-keto phospholane 23 in 22% overall yield. Thus, the later sequence is preferred on the basis of yield and availability of many α,β -unsaturated carbonyl compounds.

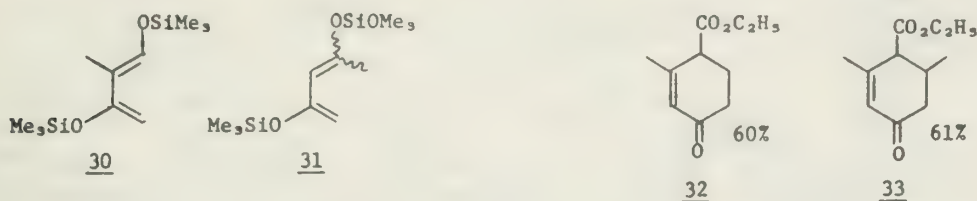
Recently, Koch²¹ prepared 2,3-bis(trimethylsilyloxy)-1,3-butadiene from dimethyl succinate according to the method of Bloomfield²² as a precursor to 4,5-dimethoxyphthalate (m-hemipinic acid). The diene 24 reacted in Diels-Alder fashion with a number of dienophiles including dimethyl acetylenedicarboxylate 25 as illustrated below.



Subsequent oxidation with sulfur, hydrolysis to the diol, dimethylation and saponification afforded the desired phthalate in 43% yield from dimethyl succinate. This represents a significant improvement over prior methodology^{23,24} in which 3,4-dimethoxybenzoic acid (27) is converted to m-hemipinic acid (29) in 15-20% yield (below).

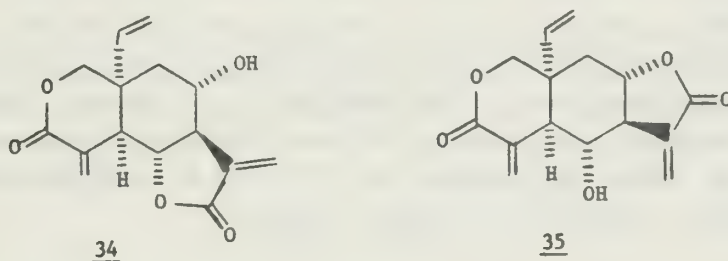


As part of an investigation directed at terpenoid synthesis, 1- and 2-methyl-1,3-bis(trimethylsilyloxy)-1,3-butadienes (30, 31) were synthesized.²⁵ Diels-Alder cycloaddition of 31 with ethyl acrylate and with ethyl crotonate afforded the cycloadducts 32 and 33, respectively, upon mild acid hydrolysis.

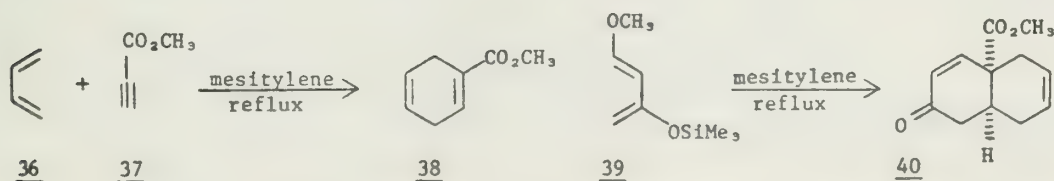


The synthesis of the keto-esters 32 and 33, useful precursors to the monoterpene pinene²⁶ and sesquiterpene ephinesol,²⁷ respectively, provides an alternative to the customarily employed methods.^{28,29} These older methods involve condensation of ethyl acetoacetate with paraformaldehyde or acetaldehyde followed by treatment with sodium ethoxide with resulting decarboxylation to afford 32 and 33, respectively. The present method is comparable in yield; however, cycloaddition reactions of additionally substituted dienes such as 30 afford adducts not available by the more classical route.

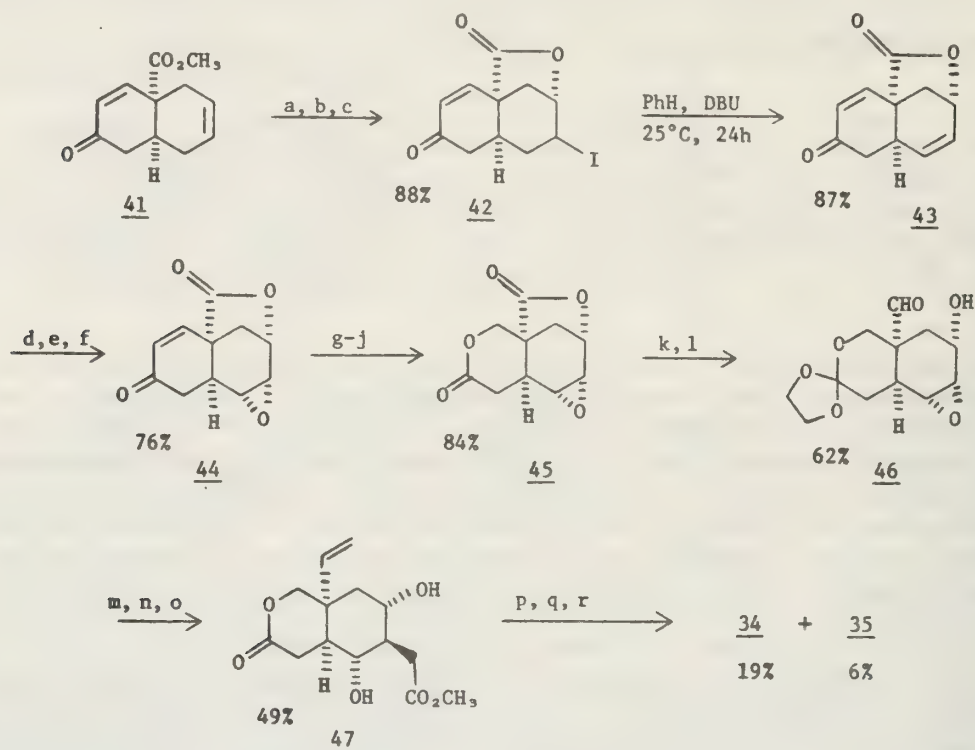
In 1977, Danishefsky reported the total synthesis of *dl*-vernolepin (34) and *dl*-vernomenin (35).³⁰ In this synthesis, the utilization of trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene resolved the obvious stereochemical requirements and allowed for the synthesis of the desired elemanolide dilactones.



A cis-fused Δ^1 -3-octalone derivative bearing angular functionality was envisioned as a suitable precursor to the desired products. In pursuit of this precursor, trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene was considered, synthesized, and found to be reactive with customarily "sluggish" dienophiles. Thus, cycloaddition of 1,3-butadiene (36) with methyl propiolate (37) afforded cycloadduct 38 which in turn functioned as a dienophile toward diene 39 to give, after acid hydrolysis, decalone 40.



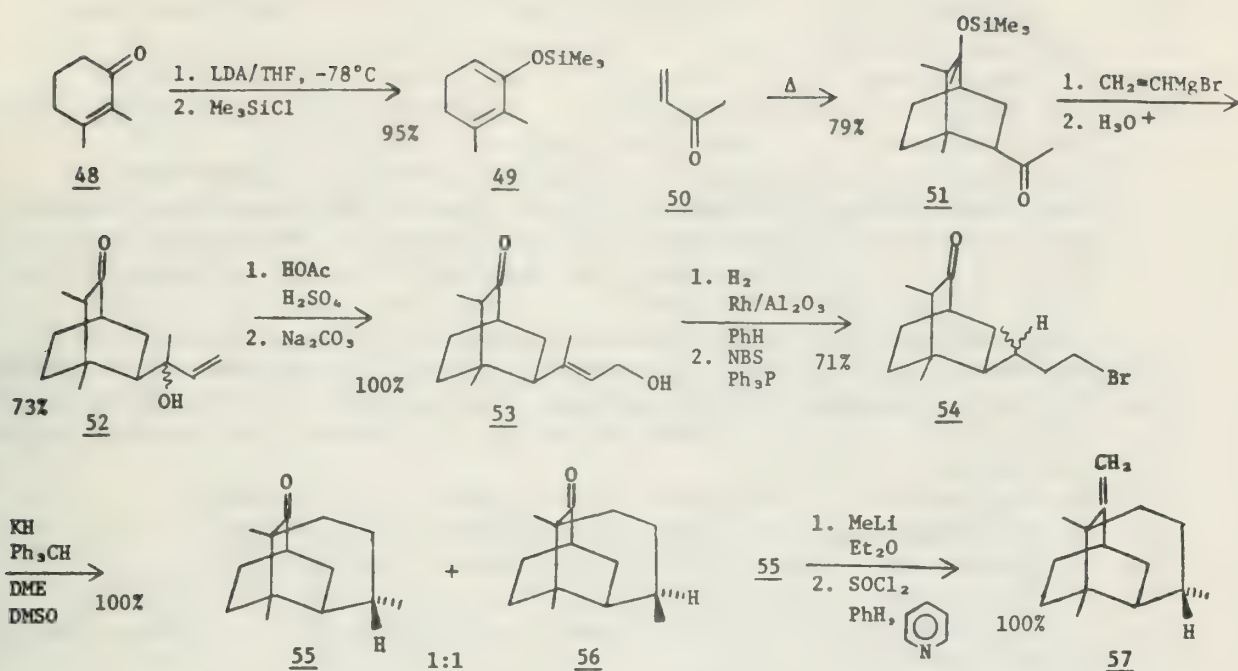
The requisite precursor now formed, the total synthesis of *dl*-vernolepin and *dl*-vernomenin proceeded as outlined below.



a) NaOH, THF-H₂O, 25°C; b) NaHCO₃, H₂O; c) I₂, KI, H₂O, 0-25°C, 48h; d) NaOH, THF-H₂O, 25°C, 1h; e) MCPBA, p-dioxane-PhH, 25°C, 10h; f) NaOAc, Ac₂O, 80°C, 3h; g) OsO₄, BaCl₂O₆, THF-H₂O, 47°C, 3h; h) Pb(OAc)₄, MeOH-PhH, 25°C, 6h; i) Lithium tri-*tert*-butoxyaluminum hydride, THF, -10°C, 20min; j) Amberlite, PhH, reflux, 6h; k) ethylene glycol, MgSO₄, p-TsOH, PhH, 80°C, 5h; l) diisobutylaluminum hydride, DME, PhCH₃, -76°C, 10min, 25°C, 15min, NaHCO₃; m) Ph₃PCH₂, DME, 0°C, 1h, 25°C, 2h, NaHCO₃; n) LiCH₂CO₂Li, DME, 56°C, 40h, H₂O; o) CH₂N₂; p) PhH, p-TsOH, 80°C; q) LDA, CH₂=N⁺(CH₃)₂, CH₃I; r) NaHCO₃

A number of low yield syntheses of the tricyclic sesquiterpene Seychellene have been reported.³¹⁻³⁴ The direct and efficient total synthesis of Seychellene is illustrative of the synthetic utility of 2-silyloxydienes.

The requisite bicyclo[2.2.2]octane system was constructed in the initial step with appropriately positioned functionality allowing for the facile final ring closure. Thus, the silyloxydiene 49 was reacted with ketone 50 to afford the endo Diels-Alder adduct. Seychellene (57) was subsequently afforded in 20% yield from the silyloxydiene as illustrated below.



Prior to the present synthesis, the most directly comparable approach to Seychellene³² was effected by appropriate elaboration of the ketone obtained from a mixture of the endo- and exo-cycloadducts formed upon reaction of 1,3-dimethyl-1,3-cyclohexadiene with methyl vinyl ketone.³⁵ This synthetic sequence is less attractive, requiring oxidation and methylation at the double bond of the initial bicycloadduct.

In summary, several groups have utilized silyloxydienes for improved entry into a variety of cyclic compounds. In view of the availability and reactivity as well as the regiochemistry and ready functionalization of their cycloadducts, silyloxydienes will undoubtedly continue to be shown as useful in synthesis.

BIBLIOGRAPHY

1. H. O. House, L. J. C. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
2. M. Rathke and D. F. Sullivan, *Syn. Commun.*, **3**, 67 (1973).
3. A. Bozuin, J. Dunagues, and M. Le Fort, *Chem. Abstr.*, **65**, 5487d (1966).
4. H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965).
5. M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976).
6. C. Girard and J. M. Conia, *Tetrahedron Lett.*, 3327 (1974).
7. K. N. Houk, *J. Am. Chem. Soc.*, **95**, 14092 (1973).
8. I. Fleming, "Frontier Orbitals and Organic Chemical Reactions, Wiley, London and New York, 1976.
9. A. S. Onishchenko, "Diene Synthesis", Israel Program of Scientific Translations, Daniel Davy and Co., New York, 1964.
10. J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
11. Yu A. Titov, *Russ. Chem. Rev.*, **31**, 267 (1962).
12. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).
13. H. O. House, W. F. Gannon, R. S. Ro, and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 1463 (1960).
14. S. Danishefsky, R. K. Singh, and R. B. Gammill, *J. Org. Chem.*, **43**, 379 (1977).

15. S. Danishefsky, M. P. Prisbylla, and S. Hiner, *J. Am. Chem. Soc.*, 100, 2918 (1978).
16. S. Danishefsky and T. Kitahara, *J. Org. Chem.*, 40, 538 (1975).
17. For other uses of silyloxydienes in synthesis see: (a) J. Banville and P. Brassard, *J. Chem. Soc. Perkin I*, 1852 (1976); (b) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, 98, 3028 (1976); (c) S. Danishefsky, R. K. Singh, and T. Harayama, *ibid.*, 99, 5810 (1977); (d) S. Danishefsky and P. M. McCurry, *J. Org. Chem.*, 42, 1819 (1977); (e) S. Danishefsky, R. K. Singh, and R. B. Gammill, *J. Org. Chem.*, 43, 379 (1978); (f) C. Girard and J. M. Conia, *Tetrahedron Lett.*, 3327 (1974); (g) T. Ibuka, Y. Mori, and Y. Inubushi, *ibid.*, 3169 (1976); (h) S. Murai, I. Ryy, Y. Kadono, H. Katayama, K. Kondo, and N. Sonoda, *Chem. Lett.*, 1219 (1977); (i) G. M. Rubottom and D. S. Krueger, *Tetrahedron Lett.*, 611 (1977).
18. L. D. Quin and J. A. Caputo, *Chem. Commun.*, 1463 (1968).
19. W. B. McCormack, U.S. Patents 2,663,636, 2663,637 (1953).
20. C. Symmes and L. D. Quin, *J. Org. Chem.*, 41, 238 (1976).
21. D. R. Anderson and T. H. Koch, *J. Org. Chem.*, 43, 2726 (1978).
22. J. J. Bloomfield, H. M. Frey, and J. Metcalfe, *Int. J. Chem. Kinet.*, 3, 85 (1971).
23. H. R. Arthur and Y. L. Ng, *J. Chem. Soc.*, 3094 (1959).
24. G. A. Edwards, W. H. Perkins, and F. W. Stoyale, *J. Chem. Soc.*, 195 (1925).
25. T. Ibuka, Y. Ito, Y. Mori, T. Aoyama, and Y. Inubushi, *Syn. Commun.*, 7, 131 (1977).
26. M. T. Thomas and A. G. Fallis, *J. Am. Chem. Soc.*, 98, 1227 (1976).
27. M. Mongrain, J. Lafontaine, A. Beloanger, and P. Deslongchamps, *Can. Jour. Chem.*, 48, 3273 (1970).
28. A. J. B. Edgar, S. H. Harper, and M. A. Kzai, *J. Chem. Soc.*, 1083 (1957).
29. E. C. Horning, M. O. Denekas, and R. E. Field, *J. Org. Chem.*, 9, 547 (1944).
30. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheridge, *J. Am. Chem. Soc.*, 99, 6066 (1977).
31. E. Piers, R. W. Britton, and W. de Waal, *J. Am. Chem. Soc.*, 93, 5113 (1971).
32. K. J. Schmalzl and R. N. Mirrington, *Tetrahedron Lett.*, 3219 (1970).
33. N. Fukamiya, M. Kato, and A. Yoshikoshi, *Chem. Commun.*, 1210 (1971).
34. G. Frater, *Helv. Chim. Acta*, 57, 172 (1974).
35. M. E. Jung and C. A. McCombs, *J. Am. Chem. Soc.*, 100, 5207 (1978).
36. R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, 8, 2358 (1969).

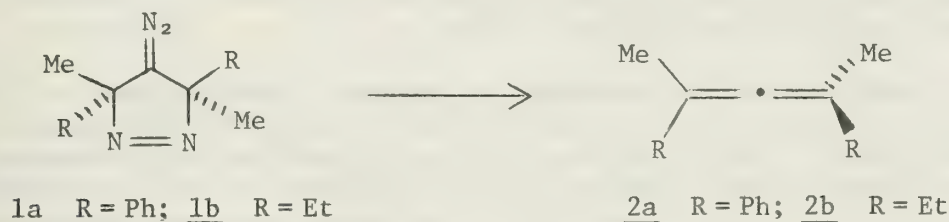
A CYCLOELIMINATIVE APPROACH TO OPTICALLY ACTIVE ALLENES:
SYNTHESIS AND DECOMPOSITION OF SOME CHIRAL DIAZOPYRAZOLINES

Reported by Dennis Hoover

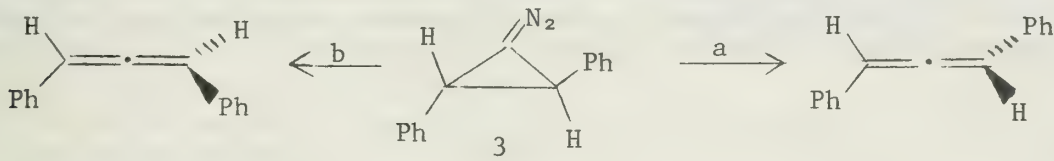
November 2, 1978

In the century which has passed since van't Hoff's prediction that allenes could exist in two enantiomeric forms,^{1e} chemists have expended considerable effort to obtain optically active allenes. In spite of this effort, few schemes have been notably successful.

Diazopyrazolines 1, generated by oxidation of the corresponding hydrazones, efficiently produce allenes by cycloelimination of nitrogen.² This reaction is of interest not only as one of the few reported syntheses



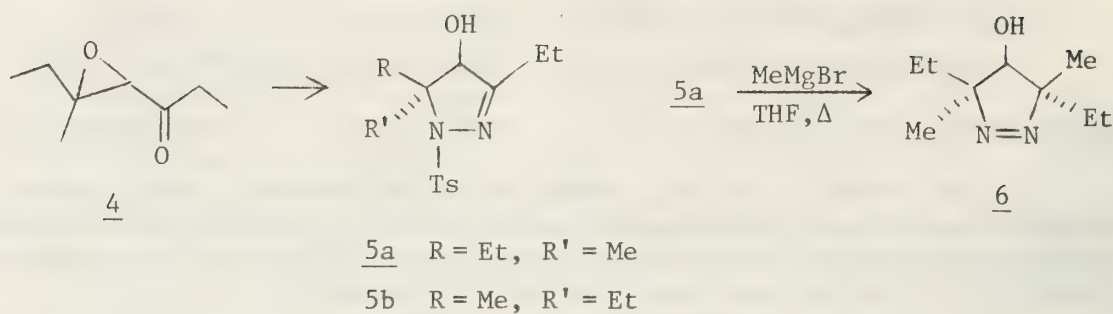
of tetrasubstituted allenes,^{1a-c} but also as a source of such optically active allenes, compounds which hitherto have been virtually inaccessible.^{1a-d,3} This potential is suggested by a mechanistic similarity between this reaction and the decomposition of diazocyclopropane 3.^{4a} Jones has obtained



several optically active allenes from optically active cyclopropanes such as 3, and proposes that retention of optical activity in the ring opening stems from a steric preference of conrotation a over conrotation b, thus leading to an excess of one allene enantiomer. A minor electronic effect has also been demonstrated.^{4b}

Investigation of the pyrazoline cycloelimination has shown that similar factors are operative in controlling the stereochemical course of allene formation in this case as well. Optically pure pyrazoline 1a affords allene 2a of presumably high, but unknown optical purity.⁵ Efforts to examine the stereochemistry of this reaction for other pyrazolines 1 have been thwarted by three obstacles:^{5,6} (1) there is no general synthetic approach to the tetrasubstituted pyrazolines, (2) a dependable method for their optical resolution has not been reported, and (3) a suitable procedure for the determination of the optical purity of the allenes produced needs to be developed.

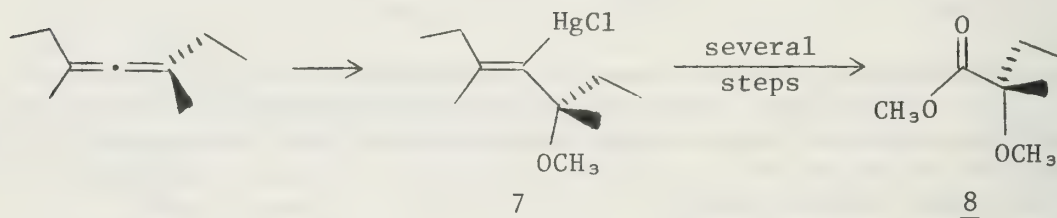
Recently, progress has been made on all three problems.⁷ The synthesis of resolved pyrazoline 6 from 4 illustrates a new route to these 1-pyrazolines.⁸ Reaction of tosylhydrazine and the ketoepoxide⁹ 4 provides a mixture of diastereomeric pyrazolols 5. Oxidation of this mixture to pyrazolone followed by selective reduction affords stereo-homogenous 5a. This racemic alcohol is resolved by liquid chromatographic separation of its diasteromeric 1-(1-naphthyl)ethyl carbamates,¹⁰ which



are individually converted by silanolysis¹¹ to the separate enantiomers. Nucleophilic addition by methylmagnesium bromide proceeds stereospecifically to generate the optically pure pyrazolol 6¹² which is converted to diazopyrazoline 1b in high yield.

The scope of this synthesis is currently being examined. The cyclization reaction appears quite general and a variety of tosylpyrazolines have been prepared. These compounds are an attractive entry into the little known 4-hydroxypyrazoline system, because they are suitably functionalized for a variety of transformations. New pyrazoline chemistry is being developed in search of an alternative method for conversion of tosylpyrazolines into the sterically congested tetrasubstituted pyrazolines.

Determination of the optical purity of allenes is a difficult problem for which there are few reliable solutions.^{1a} Recently, Pirkle and Boeder¹³ have measured allene optical purity by using a chiral NMR solvent to evaluate the configurational purity of a methoxymercurial which is obtained stereospecifically from the allene. As mercurials such as 7, which are



obtained from tetrasubstituted allenes, fail to show the required NMR nonequivalence, a sequence has been developed to convert the mercurial to methyl ester 8 without racemization. The optical purity and absolute configuration of 8 are readily established spectroscopically by the chiral solvent method.¹⁴

Summary. Solid groundwork has thus been laid for further investigation of this reaction. A combination of the synthetic chemistry described and that being developed will provide resolvable 1-pyrazolines with substituents of varying steric bulk and electronic character. Determination of the optical purity of the allenes produced via the method discussed will reveal the importance of these factors in determining the stereochemistry of the cycloelimination.

BIBLIOGRAPHY

1. (a) For a review of chiral allenes, see R. Rossi and P. Diversi, *Synthesis*, 25 (1973); (b) D. R. Taylor, *Chem. Rev.*, 67, 317 (1967); (c) P. J. Stang and R. J. Hargrove, *J. Org. Chem.*, 40, 657 (1975); (d) W. H. Pirkle and C. W. Boeder, *J. Org. Chem.*, 43, 2091 (1978); (e) J. H. van't Hoff, "La Chimie dans l'Espace", P. M. Bazendijk, Rotterdam, 1875, p. 29.
2. R. Kalish and W. H. Pirkle, *J. Am. Chem. Soc.*, 89, 2781 (1967).
3. The first optically active allene reported was a tetrasubstituted allene obtained by dehydration of an allylic alcohol with an optically active acid: P. Maitland and W. H. Mills, *Nature*, 135, 994 (1935).
4. (a) W. M. Jones, J. M. Walbrick, and J. W. Wilson, Jr., *J. Am. Chem. Soc.*, 90, 2895 (1968), and references therein; (b) W. M. Jones and D. L. Krause, *J. Am. Chem. Soc.*, 93, 551 (1971).
5. R. J. Convers, Ph.D. Thesis, University of Illinois, Urbana, Illinois, 1974.
6. K. A. Thornburg, Ph.D. Thesis, University of Illinois, Urbana, Illinois, 1970.
7. D. Hoover and W. H. Pirkle, unpublished results.
8. For two alternate approaches, see: W. L. Mock, *Dissert. Abstr.*, 26, 6374 (1966), and reference 5.
9. Only four trisubstituted 1-p-tosyl-4-hydroxypyrazolines have been reported: D. P. G. Hamon and H. Holding, *J. Chem. Soc. Chem. Commun.*, 1330 (1970). Other such cyclizations are known: O. Widman, *Ber.*, 49, 477, 2778 (1916); H. Jorlander, *Ber.*, 49, 2782 (1916); S. Bodforss, *Ber.*, 49, 2795 (1916); A. Padwa, *J. Org. Chem.*, 30, 1274 (1965); D. N. Dhar and R. C. Munjal, *Z. Naturforsch.*, 28b, 369 (1973); W. A. Hutchins, D. C. Motwani, K. D. Mudbhatkal, and T. S. Wheeler, *J. Chem. Soc.*, 1882 (1938); N. H. Cromwell and R. A. Setterquist, *J. Am. Chem. Soc.*, 76, 5752 (1954).
10. For a discussion of reasons underlying the separability of diastereomeric carbamates, see: W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, 42, 1839 (1977).
11. W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, 42, 2781 (1977).
12. A similar reaction forming 3,3,5,5-tetramethyl-1-pyrazoline in low yield has been independently reported: P. S. Engel, R. A. Hayes, L. Kiefer, S. Szilagyi, and J. W. Timberlake, *J. Am. Chem. Soc.*, 100, 1876 (1978).
13. W. H. Pirkle and C. W. Boeder, *J. Org. Chem.*, 42, 3697 (1977).
14. For a discussion and application of this method, see: W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, 42, 384 (1977).

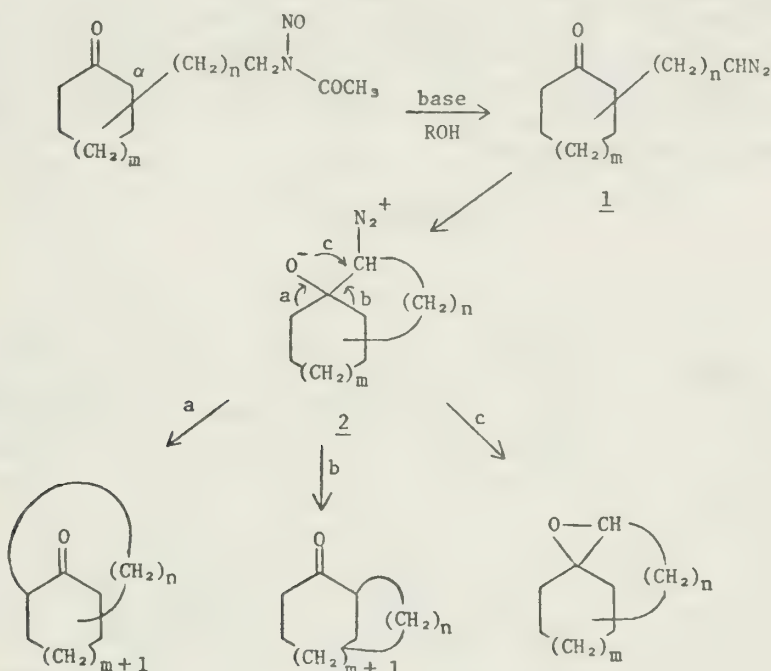
INTRAMOLECULAR DIAZOALKANE CARBONYL INSERTIONS

Reported by Paula Roach

November 6, 1978

The synthesis of novel ring systems has long been a goal of the organic chemist. Many methods have been devised to accomplish this end; one that has found application in both natural product and theoretical studies is diazoalkane ring expansion. Diazomethane attack on cycloalkanones and subsequent rearrangement to one carbon homologated ketones has been well documented.¹ As an improvement over intermolecular methods,² Gutsche and co-workers have constructed new or difficult ring systems by intramolecular diazoalkane insertions.^{3,4} Treatment of side chain N-nitroso amides or urethanes with alcoholic base generates the diazoalkane 1 (Scheme I) which collapses to a charge separated intermediate 2. Anti displacement of the

Scheme I



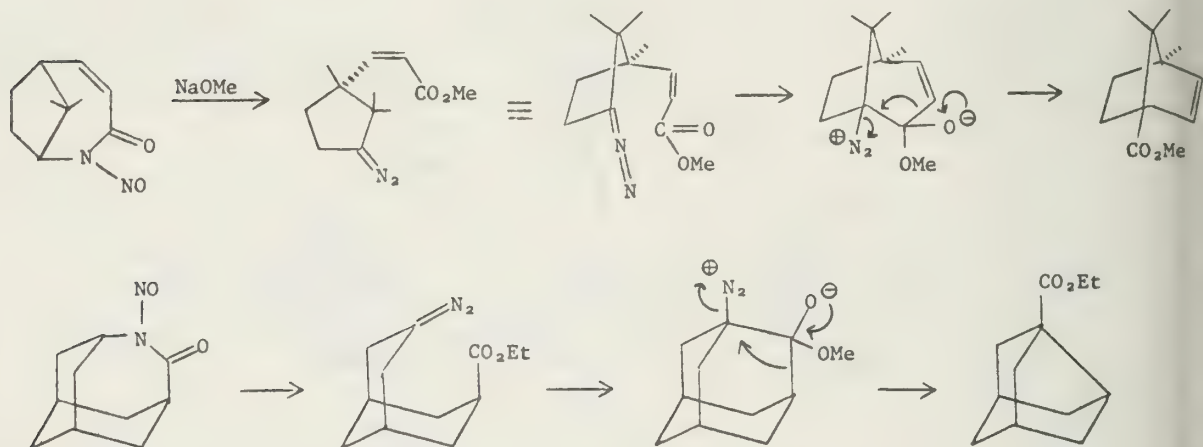
nitrogen by migrating carbon forms the new skeleton and regenerates the ketone (path a,b). If oxygen is anti to nitrogen, epoxides may be formed (path c). Since N-nitroso amides can also form diazonium ions, carbonium ion products such as ethers and olefins are often also isolated.⁵ The reactions are usually carried out in $K_2CO_3/MeOH$ or $EtONa/EtOH$ at room temperature or at reflux and afford 60-95% of rearranged ketones, often as a single isomer.

The predominant isomer is the result of antiperiplanar displacement of nitrogen in the most stable zwitterion, and this is determined by the relative transition states from diazoalkanone to zwitterion. The type of ring system formed, steric interactions, minimum charge separation, and, in flexible systems, conformational preferences are all important factors in deciding which transition state will have the lowest energy; for example, when a two carbon side chain ($n=1$) is in the α position, no rearrangement products are isolated, perhaps because a four membered ring

would be formed in the zwitterion; however, if the side chain is in the β or γ position, 50-65% of rearranged ketones is found.^{4,14,16} Although cyclopentanone ($m=0$) with an α four carbon side chain ($n=3$) and cyclohexanone ($m=1$) with an α three carbon side chain ($n=2$) both form a five-six membered ring zwitterion, conformational preferences can account for the fact that the former gives a 2:1 ratio of fused and bicyclic ketones (99% isolated yield) and the latter gives bicyclic ketone (80% isolated yield) as a single isomer. In the latter, the addition of methyl groups α to the carbonyl and/or on the diazoalkane side chain reduces the amount of ketone and increases the amount of epoxide isolated.⁶ This has been explained by Gutsche as steric approach control where the diazoalkane acts as an electrophile, attacking the less hindered oxygen; however, conformational changes caused by addition of the alkyl groups can adequately explain the change in products.

Although esters are usually unreactive toward intramolecular diazoalkane insertions,⁹ such a reaction has been observed in two cases where a rigid carbon skeleton holds the diazo and ester functions in close proximity (Scheme II).^{10a-d} The reaction mechanism and products are considered to be completely analogous to ketone insertions. Epoxide formation by diazoethane attack on a lactone has also been noted.¹¹ It was found that this would only occur when the lactone was doubly activated by electron-withdrawing groups.

Scheme II



Paquette has attempted transannular diazoalkane insertions in cyclo-dodecanes; however, in contrast to transannular aldol condensations, no ring contracted material was isolated.¹² Diazoalkane insertions have been mentioned in synthetic strategies,¹³ and have been applied in the syntheses of veatchine,¹⁴ zizaene,¹⁵ and prezizaene.¹⁶

BIBLIOGRAPHY

1. C. D. Gutsche, *Org. Reactions*, **8**, 364 (1954).
2. (a) C. D. Gutsche and T. D. Smith, *J. Am. Chem. Soc.*, **82**, 4067 (1960); (b) J. W. Baum and C. D. Gutsche, *J. Org. Chem.*, **33**, 4312 (1968); (c) T. Miwa, M. Kato, and T. Tamano, *Tetrahedron Lett.*, 1761 (1969); (d) J. D. Henion and D. G. I. Kingston, *J. Org. Chem.*, **38**, 3067 (1973); (e) For a correction of (2a), see C. H. DePuy and J. L. Marshall,

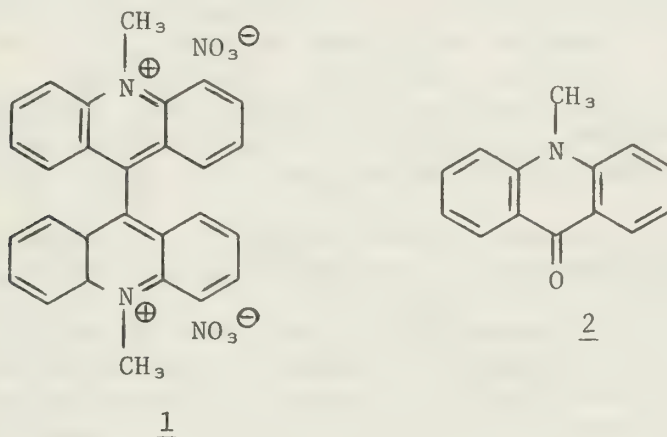
- J. Org. Chem., 33, 3326 (1968) and J. R. Wiseman and H.-F. Chan, J. Am. Chem. Soc., 92, 4749 (1970).
3. C. D. Gutsche and D. M. Bailey, J. Org. Chem., 28, 607 (1963).
 4. D. M. Bailey, J. E. Bowers, and C. D. Gutsche, J. Org. Chem., 28, 610 (1963).
 5. (a) W. R. Bamford and T. S. Stevens, J. Chem. Soc., 4735 (1952);
(b) J. W. Powell and M. C. Whiting, Tetrahedron, 5, 305 (1959);
(c) L. Friedman and H. Schechter, J. Am. Chem. Soc., 81, 5512 (1959).
 6. C. D. Gutsche and J. E. Bowers, J. Org. Chem., 32, 1203 (1967).
 7. C. D. Gutsche and H. H. Peter, J. Am. Chem. Soc., 77, 5971 (1955).
 8. J. N. Bradley, G. W. Cowell, and A. Ledwith, J. Chem. Soc., 3433 (1964).
 9. C. D. Gutsche and I. Y. C. Tao, J. Org. Chem., 32, 1778 (1967).
 10. (a) I. Fleming and R. B. Woodward, J. Chem. Soc., 1653 (1973); (b) E. H. Billet and I. Fleming, *ibid.*, 1658 (1973); (c) E. H. Billet, I. Fleming, and S. W. Hanson, *ibid.*, 1661 (1972); (d) I. Fleming and S. W. Hanson, *ibid.*, 1669 (1973).
 11. F. M. Dean and B. K. Park, J. Chem. Soc., Perkin I, 1260 (1976).
 12. L. A. Paquette and M. Lee Wise, Tetrahedron, 24, 2937 (1968).
 13. D. P. G. Hamon and R. N. Young, Aust. J. Chem., 29, 145 (1976).
 14. K. Wiesner, S. Uyeo, A. Philipp, and Z. Valenta, Tetrahedron Lett., 6279 (1968).
 15. R. M. Coates and R. L. Sowerby, J. Am. Chem. Soc., 94, 5386 (1972).
 16. R. M. Coates and P. M. Roach, unpublished results.

MECHANISTIC STUDIES OF THE LUCIGENIN SYSTEM

Reported by Michael J. Darmon

November 9, 1978

Lucigenin (10,10'-dimethyl-9,9' biacridinium dinitrate, $\text{DBA}^{2+} \cdot 2\text{NO}_3^-$, 1) has stood for years in relative isolation in the class of man-made organic chemiluminescent compounds.¹ Although it was one of the earliest molecules observed to chemiluminesce, numerous investigations have not provided a convincing mechanism for that process.²



The many mechanisms that have been proposed over the years have been repeatedly modified or replaced as new information became available. The early studies were uncertain even in the nature of the emitting species. Only recently has it been proven that the primary degradation product, N-methyl acridone (NMA, 2) (λ_{max} , 442 nm) was the excited molecule providing a green fluorescence at ca. 440 nm.^{3,4} The thorough study by Janzen provides a basis for determining the mechanism.⁵ Janzen observed three radical components by ESR studies of lucigenin in hydroxylic aqueous dimethyl sulfoxide solutions. Two of these have been identified as DBA^+ and the ketyl, NMA^- . By incorporating important data from previous studies, three highly plausible interrelated mechanisms were proposed. Two mechanisms proceeded by a biacridan dioxetane and are believed to be responsible for the immediate bright luminescence observed. Direct production of this dioxetane with singlet oxygen at -78°C lends support to this mechanism.⁶ The observed delayed luminescence is accredited to the NMA^- intermediate. In a separate study, chemiluminescence was observed from NMA and O_2^- involving the generation of NMA^- .⁷ White,⁸ McCapra⁹ and others studying simpler acridine and acridan model systems have discovered that many of the intermediates in the chemiluminescent reactions of these systems mimic those found in lucigenin.

In many cases the presence of reducing agents such as metal ions¹⁰ or organic molecules such as fructose¹¹ have been shown to increase the rate of luminescence. Cyclic voltametry has been employed by Hercules to investigate some of the possible redox reactions which might be involved.¹² By reexamining the lucigenin system with several nucleophiles and correlating data on some similar systems, Maeda has developed a reduction mechanism of lucigenin which involves the diradical of dimethylbiacridene as an intermediate.^{13,14}

Over four decades of research by many prominent investigators has gone into the lucigenin system and the mechanism of lucigenin chemiluminescence is still to be fully developed. However, studies during the last ten years have uncovered and linked many of the intermediates into a more complete description of the chemiluminescent mechanism.

BIBLIOGRAPHY

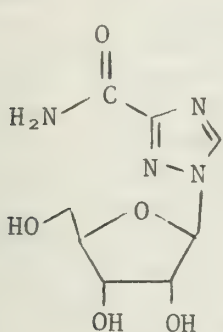
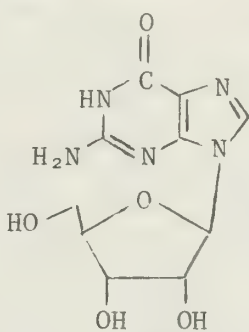
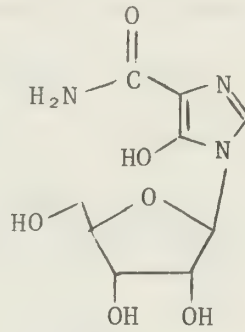
1. K. Gleu and W. Petsch, *Angew. Chem.*, 48, 57 (1935).
2. R. M. Acheson, "Acridines", Wiley Interscience Publisher, New York, 1973, p. 615; F. McCapra, *Prog. Org. Chem.*, 8, 231 (1973).
3. K. Maeda and T. Hayashi, *Bul. Chem. Soc. Jap.*, 40, 169 (1967).
4. J. R. Totter, *Photochem. Photobiol.*, 3, 231 (1964).
5. E. G. Janzen, J. B. Pickett, J. W. Happ, and W. DeAngelis, *J. Org. Chem.*, 35, 88 (1970); J. W. Happ and E. G. Janzen, *ibid.*, 35, 96 (1970); J. W. Happ, E. G. Janzen, and B. C. Rudy, *ibid.*, 35, 3382 (1970).
6. K. W. Lee, L. A. Singer, and K. D. Legg, *J. Org. Chem.*, 41, 2685 (1976); J. Nikokavouras, A. Vavayannis, and G. Vassilopoulos, *J. Prakt. Chem.*, 320, 43 (1978).
7. I. Rosenthal and T. Bercovici, *J. Chem. Soc. Commun.*, 200 (1973).
8. M. M. Rauhut, D. Sheehan, R. A. Clark, and A. M. Semsel, *Photochem. Photobiol.*, 4, 1097 (1965); E. Rapaport, M. W. Cass, and E. H. White, *J. Am. Chem. Soc.*, 94, 3153 (1972); E. Rapaport, M. W. Cass, and E. H. White, *ibid.*, 94, 3160 (1972); M. W. Cass, E. Rapaport, and E. H. White, *ibid.*, 94, 3168 (1972); M. M. Rauhut, D. Sheehan, R. A. Clarke, and A. M. Semsel, *Photochem. Photobiol.*, 4, 1097 (1965).
9. F. McCapra and D. G. Richardson, *Tetrahedron Lett.*, 43, 3167 (1964); F. McCapra, D. G. Richardson, and Y. C. Chang, *Photochem. Photobiol.*, 4, 1111 (1965); F. McCapra, *Pure Appl. Chem.*, 24, 611 (1970); F. McCapra, M. Roth, D. Hysert, and K. A. Zaklika, *Chemilum. Biolum. Pap. Int. Conf.*, 313 (1973).
10. L. I. Dubovenko and A. P. Tovmasyan, *Sov. Prog. Chem.*, 37, 83 (1971); L. I. Dubovenko and E. Y. Khotinets, *ibid.*, 37, 67 (1971); L. I. Dubovenko and A. P. Tovmasyan, *ibid.*, 39, 68 (1973); L. I. Dubovenko and A. P. Tovmasyan, *ibid.*, 39, 85 (1973); L. I. Dubovenko and A. Y. Nazarenko, *ibid.*, 41, 80 (1975); L. I. Dubovenko, L. M. Korotun, and A. P. Kostyshina, *Ukr. Khim. Zh.*, 42, 1194 (1976); L. I. Dubovenko and A. Y. Nazarenko, *ibid.*, 43, 984 (1977).
11. J. R. Totter, *Photochem. Photobiol.*, 22, 203 (1975).
12. K. D. Legg and D. M. Hercules, *J. Am. Chem. Soc.*, 91, 1902 (1969); K. D. Legg, D. W. Shive, and D. M. Hercules, *Anal. Chem.*, 44, 1650 (1972).
13. E. M. Kosower and J. L. Cotter, *J. Am. Chem. Soc.*, 86, 5524 (1964); S. F. Mason and D. R. Roberts, *Chem. Commun.*, 476 (1967); I. Agranat and Y. Tapuhi, *J. Am. Chem. Soc.*, 98, 615 (1976).
14. S. Wada, K. Maeda, and K. Nakada, *Nippon. Kagak. Kaishi*, 639 (1977).

RIBAVIRIN: STRUCTURE-ACTIVITY CORRELATIONS

Reported by David R. Haines

November 13, 1978

Ribavirin (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide, 1), synthesized in 1972 by Witkowski *et al.*,^{1,2} was the first synthetic broad-spectrum antiviral agent found to act against viral replication directly, rather than through the induction of interferon.³ Many analogs of ribavirin have since been synthesized and tested for biological activity.⁴⁻¹⁷ This abstract will discuss the mechanism of action of ribavirin and studies of the structural requirements for biological activity of similar molecules.

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The structure of ribavirin indicates hydrogen bonding and dimensional properties similar to guanosine 2, and its biological action appears to be derived from these similarities. Ribavirin-5'-monophosphate, the metabolically active species formed *in vivo*, acts predominantly through the inhibition of the enzyme inosine-5'-monophosphate (IMP) dehydrogenase, the enzyme at the biosynthetic branch point of purine synthesis which leads to guanosine synthesis.¹⁸⁻²⁴ The kinetics of this inhibition indicate nearly competitive inhibition with a K_i of 2.5×10^{-7} M (K_i for guanosine monophosphate = 2.2×10^{-4} M), while the K_m for IMP, the natural substrate, is 1.8×10^{-5} M.²⁵ Ribavirin is, therefore, a highly efficient inhibitor of guanosine synthesis. Results of other studies have indicated some inhibition of viral RNA polymerase.²⁶

Because of the high specificity and broad-spectrum activity of the ribavirin, much work has gone into defining the steric and electronic requirements for activity. Comparisons of the structures of ribavirin-5'-monophosphate to other active and inactive nucleotides indicate fairly rigid requirements for activity in the IMP dehydrogenase system. Analog studies have indicated that N-2 of the heterocyclic ring is important to, though not essential for, activity. Replacement of N-2 with C-OH, as in the antibiotic bredinin 3, produces high activity, while replacement of N-2 with a large or nonpolar group greatly reduces the activity.^{14,15}

X-ray crystal structures, coupled with extended Hückel theory calculations, suggest the necessity for stability in the high anti conformation for biological activity. NMR structural evaluations indicate similar high syn solution conformations for both active and inactive compounds (Figure 1). Ribavirin-5'-phosphate, IMP, GMP and other nucleotides known to bind to IMP dehydrogenase have a relatively stable high anti conformation, while molecules having a bulky substituent at positions 2 or 5 are unstable in this conformation and are inactive. A change of the aromatic ring from

triazole to tetrazole also favors the high syn form and produces inactive compounds.^{8,27-31}

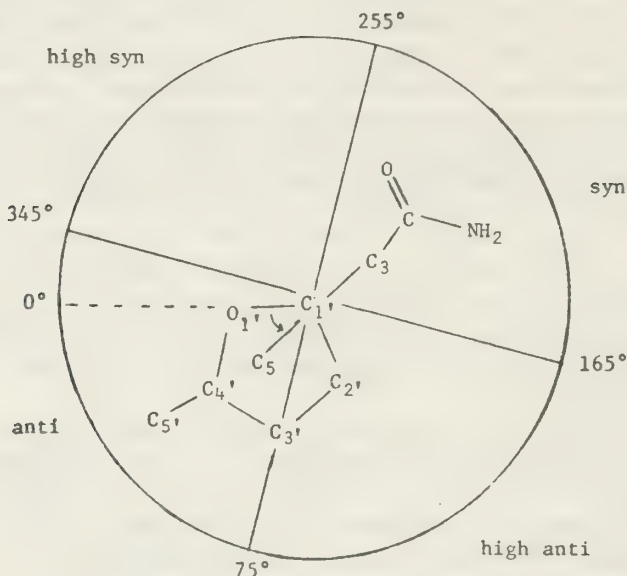


Figure 1. 0° rotation is defined as a cis planar arrangement of O₁' - C₁' - N₁ - C₅.

The studies of ribavirin, IMP, and their analogs have elucidated several steric requirements for substrates and inhibitors of IMP dehydrogenase. Ribavirin, or analogs designed according to these steric requirements, can serve as selective guanosine synthesis inhibitors without seriously affecting adenosine synthesis or other cellular functions of a normal interphase cell. Nucleosides which are sterically restricted to the high anti conformation may prove to be even more efficient antiviral agents than ribavirin. Clinical studies of ribavirin are in progress with promising preliminary results.^{32,33}

BIBLIOGRAPHY

1. J. T. Witkowski, R. K. Robins, R. W. Sidwell, and L. N. Simon, *J. Med. Chem.*, **15**, 1150-1154 (1972).
2. G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. D. Schweizer, *J. Am. Chem. Soc.*, **94**, 5894-5897 (1972).
3. L. B. Allen, J. H. Huffman, and R. W. Sidwell, *Antim. Ag. Chemother.*, **3**, 534-535 (1973).
4. L. Dudycz, D. Shugar, E. De Clercq, and J. Descamps, *J. Med. Chem.*, **20**, 1354-1356 (1977).
5. M. Fuertes, J. T. Witkowski, D. G. Streeter, and R. K. Robins, *J. Med. Chem.*, **17**, 642-645 (1974).
6. T. Huynh-Dinh, J. Igolen, E. Bisagni, J. P. Marquet, and A. Civier, *J. Chem. Soc., Perkin I*, 761-764 (1977).
7. A. S. Narang, and R. Vince, *J. Med. Chem.*, **20**, 1684-1687 (1977).
8. M. S. Poonian, E. F. Nowoswiat, J. F. Blount, and M. J. Kramer, *J. Med. Chem.*, **19**, 1017-1020 (1976).
9. M. S. Poonian and E. F. Nowoswiat, *J. Org. Chem.*, **42**, 1109-1110 (1977).
10. G. R. Revankar and R. K. Robins, *J. Hetero. Chem.*, **13**, 169-170 (1976).

11. G. R. Revankar and R. K. Robins, *Ann. NY Acad. Sci.*, 255, 167-175 (1975).
12. R. W. Sidwell, L. N. Simon, J. T. Witkowski, and R. K. Robins, *Proc. Int. Congr. Chemother.*, 8th, 1974, 3, 889-903 (1974).
13. P. C. Srivastava, G. A. Ivanovics, R. J. Rousseau, and R. K. Robins, *J. Org. Chem.*, 40, 2920-2924 (1975).
14. P. C. Srivastava, D. G. Streeter, T. R. Matthews, L. B. Allen, R. W. Sidwell, and R. K. Robins, *J. Med. Chem.*, 19, 1020-1026 (1976).
15. P. C. Srivastava, M. V. Pickering, L. B. Allen, D. G. Streeter, M. T. Campbell, J. T. Witkowski, R. W. Sidwell, and R. K. Robins, *J. Med. Chem.*, 20, 256-262 (1977).
16. J. T. Witkowski, R. K. Robins, G. P. Khare, and R. W. Sidwell, *J. Med. Chem.*, 16, 935-937 (1973).
17. J. T. Witkowski, M. Fuertes, P. D. Cook, and R. K. Robins, *J. Carb-Nucl.*, 2, 1-36 (1975).
18. D. G. Streeter, L. N. Simon, R. K. Robins, and J. P. Miller, *Biochemistry*, 13, 4543-4550 (1974).
19. J. P. Miller, L. J. Kigwana, D. G. Streeter, R. K. Robins, L. N. Simon, and J. Roboz, *Ann. NY Acad. Sci.*, 284, 211-229 (1977).
20. D. G. Streeter, J. P. Miller, R. K. Robins, and L. N. Simon, *Ann. NY Acad. Sci.*, 284, 201-210 (1977).
21. L. B. Allen, K. H. Boswell, T. A. Khwaja, R. B. Meyer, R. W. Sidwell, and J. T. Witkowski, *J. Med. Chem.*, 21, 742-746 (1978).
22. C. M. Smith, L. J. Fontenelle, H. Muzik, A. R. P. Paterson, H. Unger, L. W. Brox, and J. F. Henderson, *Biochem. Pharm.*, 23, 2727-2735 (1974).
23. P. Scheffler, D. Haghchenas, and R. Wigand, *Acta Virol.*, 19, 106-115 (1975).
24. J. K. Lowe, L. Brox, and J. F. Henderson, *Cancer Res.*, 37, 736-743 (1977).
25. D. G. Streeter, J. T. Witkowski, G. P. Khare, R. W. Sidwell, R. J. Bauer, R. K. Robins, and L. N. Simon, *Proc. Nat. Acad. Sci., USA*, 70, 1174-1178 (1973).
26. C. Scholtissek, *Arch. Virol.*, 50, 349-352 (1976).
27. P. Prusiner and M. Sundaralingam, *Nature (New Biology)*, 244, 116-118 (1973).
28. P. Dea, M. P. Schweizer, and G. P. Kreishman, *Biochemistry*, 13, 1862-1867 (1974).
29. D. L. Miles, D. W. Miles, P. Redington, and H. Eyring, *Proc. Natl. Acad. Sci. USA*, 73, 4257-4260 (1976).
30. P. Prusiner and M. Sundaralingam, *Acta Cryst.*, B32, 419-426 (1976).
31. D. L. Miles, D. W. Miles, and H. Eyring, *Biochim. Biophys. Acta*, 518 (1978).
32. P. A. A. Galvao and I. O. Castro, *Ann. N. Y. Acad. Sci.*, 284, 278 (1977).
33. F. Salido-Rengell, H. Nassar-Quinones, and B. Briseno-Gracia, *Ann. N. Y. Acad. Sci.*, 284, 272 (1977).

ORGANIC SUPERCONDUCTORS

Reported by Bill Roper

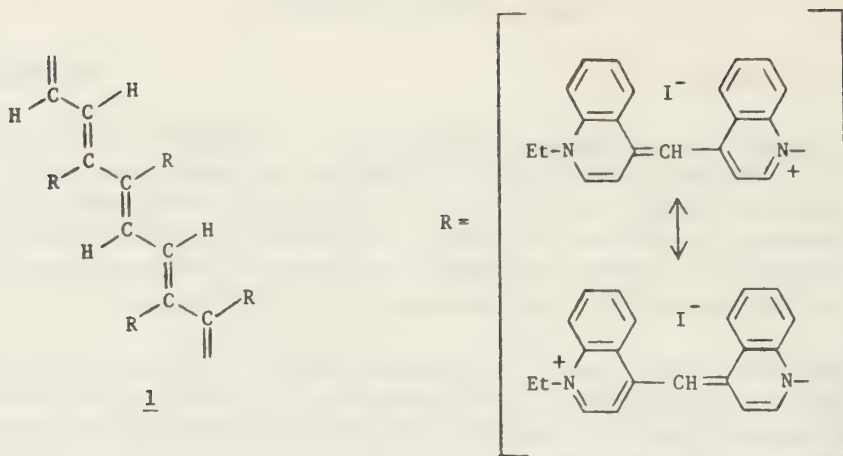
November 16, 1978

1. Introduction to Superconductivity. The phenomenon of superconductivity or persistent currents in which the resistance of a material becomes vanishingly small has been the subject of considerable interest since its discovery by Onnes in 1911.¹ Although a mathematical treatment of superconductivity has been achieved, a qualitative understanding of the phenomenon is sufficient for the purposes of this seminar.

The Ginzburg-Landau theory of superconductivity describes the superconducting state in terms of a wave function, ψ , similar to the description of electron-orbital interactions by the Schrodinger equation.² Bardeen, Cooper, and Schrieffer proposed a microscopic theory of superconductivity that explains, on the electronic level, some of the assumptions made by the Ginzburg-Landau theory.³ The BCS theory proposes that a current flow in a superconducting material causes small time-dependent distortions of the material's crystal lattice; in the case of the more common metallic superconductors, these lattice elements are the positively charged metal atoms. These distortions, in turn, lead to the formation of electron pairs, termed Cooper pairs,⁴ through a lattice-induced electron-electron attraction. At low temperatures, around 20°K or below, this interaction is sufficiently strong so as to be unaffected by the thermal motion of the electrons. The temperature where the electron-electron attraction becomes dominant is known as the transition temperature for the material or the critical temperature for superconductivity. The BCS theory places a further restriction on the system in that it requires that the momentum of the center of mass of any Cooper pair be equal to the momentum of every other pair of electrons. This restriction serves to prevent current decay in the superconducting system as, in order for decay to occur, a very large number of electron pairs must simultaneously move from the higher energy state of current flow to the ground state of no current flow; that action is highly forbidden. Current decay could also occur via unpairing of the electrons; however, the resultant loss of stabilization due to the unpairing prevents current decay via this path.

It can be seen qualitatively that the greater the mass of the positively charged lattice elements in a superconductor, the smaller the lattice distortions resulting from a current flow in the material, and thus the smaller the stabilization energy gained through formation of Cooper pairs. Conversely, a lattice element of very low mass would produce a very large electron-electron attractive force, perhaps strong enough to permit superconductive phenomena to be observed at relatively high temperatures, possibly at room temperature or above.

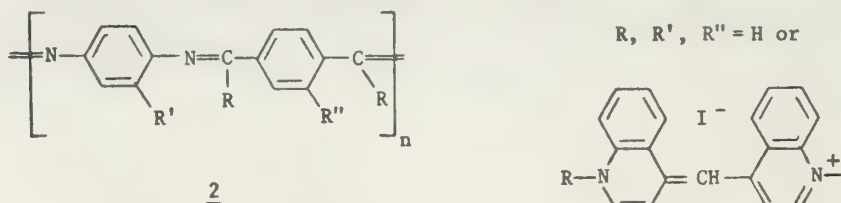
2. Little's Polymer - A Model for an Organic Superconductor. It was in attempts to design a system that would be superconducting at high temperatures that Little first proposed the possibility of an organic superconductor (1).^{5,6}



Little postulated that a current could be carried along the conjugated polyene spine of the polymer. This current flow would result in a time-dependent polarization of the cyanine dye side chains as electrons passed the substituent positions just as current flow in superconductors produces small lattice distortions. However, since electrons are much lower in mass than atoms, a correspondingly greater distortion of charge distribution is possible. This large polarization would result in a greater attraction between the electron pairs traveling along the spine of the polymer and thus a correspondingly higher transition temperature for the system. Little's calculations showed that if the pi system of the conjugated polyene was totally delocalized, the transition temperature for the molecule would be in the neighborhood of 2200°K.

Even if the pi bonds are localized in such a polymer, Little predicted that the molecule might be superconducting at temperatures of several hundred degrees Kelvin. This would require that the energy difference between the insulating band, filled with electrons, and the conducting band, empty or partially filled with electrons, in the crystal be less than 0.67 eV, and that this gap also be less than the difference in energy between the polarized and unpolarized states of the side chains. Somewhat later, Little pointed out that if the individual polymer molecules were about 100 Å in length, the polymer should exhibit bulk superconductive properties through Josephson tunneling, electron pairs crossing thin insulating layers between superconductive domains, between the molecules of polymer.⁷ This tunneling phenomenon has been well characterized in inorganic superconductors.⁸

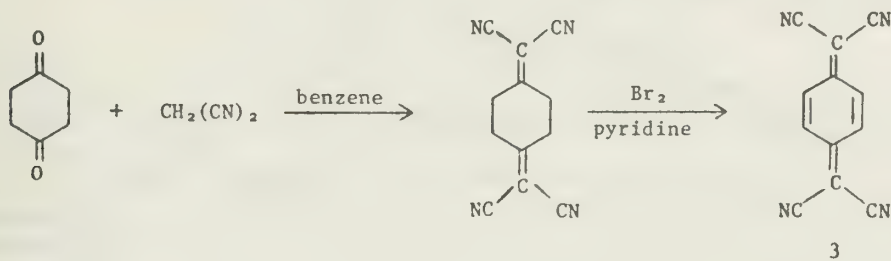
Little's polymer has not yet been synthesized, although a number of attempts have been made to synthesize similar systems.⁹⁻¹¹ For instance, Hodgkin *et al.* tried to synthesize the Schiff-base polymer 2.⁹



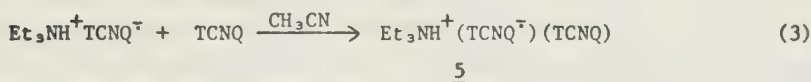
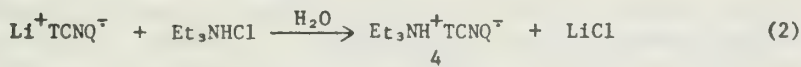
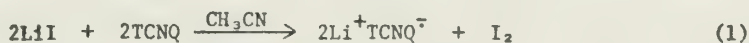
Unfortunately, these polymers tend to be insoluble in the solvents used for the polymerization reaction and precipitate out at low molecular weights. Melt polymerization produces complex ill-defined products.

Little's work has been the subject of considerable criticism. Paulus pointed out that, since the electrons of the polarized side chain will tend to shift back to their normal distribution on the same time scale as the current-carrying electrons move along the spine of the molecule, the electron-electron distance would have to be extremely small in order for the charge induced electron-electron attraction to be effective.¹² This, however, would produce a large coulombic repulsion between the two electrons which would negate the stabilization produced by the formation of Cooper pairs. Later analysis by Chaikin *et al.* indicated that the electronic interactions postulated by Little would most likely result in the molecule being an insulator due to narrowing of the conduction band.^{13,14}

3. Systems Containing TCNQ. More recent attempts at the preparation of an organic superconductor have investigated the interesting properties of 7,7,8,8-tetracyanoquinodimethane (TCNQ, 3). TCNQ was first synthesized by Acker *et al.* from cyclohexane-1,4-dione and malononitrile.^{15,16}

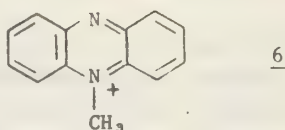


It was found that TCNQ is a strong pi acid, readily accepting an electron into the molecule's low-lying LUMO to form the radical anion. TCNQ was found to form two different series of crystalline complexes, 4 and 5, depending on the conditions under which the complex was formed.



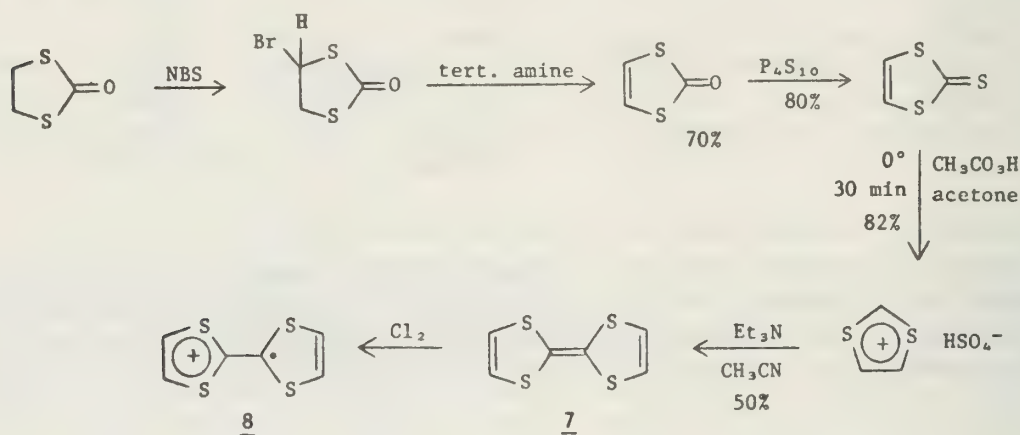
The complexes are readily distinguished by molecular weight determination. In addition, the resistivities of the different series of complexes differ considerably. Complex 4 was found to possess a relatively high resistivity of 10^3 - 10^4 ohm cm. The second type of complex, 5, contains two moles of TCNQ per mole of cation and exhibits an extremely low resistivity, 0.01-100 ohm cm. Previously, the lowest known resistivity in an organic compound was 8 ohm cm for the metastable complex of iodine and perylene.¹⁷ The resistivity of 5 was found to be highly anisotropic, varying from 10^{-2} to 10^3 ohm cm depending on the direction in which the current travels through the crystal, indicating that the conductivity is highly dependent upon the crystal structure and packing.¹⁸

Melby prepared a complex of N-methylphenazinium cation (NMP, 6) and the TCNQ radical anion.¹⁹



NMP-TCNQ was found to have a crystal structure consisting of stacks of NMP alternating with stacks of TCNQ, a highly unusual lattice arrangement.²⁰ The complex was found to be a metallic conductor at temperatures above 200°K.²¹ Comparisons of the charge transfer band for NMP-TCNQ with those of KTCNQ and Cs₂TCNQ₃²² complexes led Epstein *et al.* to the conclusion that both the polarizability of the NMP cation and the stacked crystal structure played important roles in determining the conductivity of this complex.²¹

Another class of TCNQ complexes which have been heavily investigated are its complexes with tetrathiofulvalene (TTF, 7). TTF was synthesized by Wudl *et al.* as shown below.²³⁻²⁵ It is easily oxidized to its radical cation (8) by half a molar equivalent of chlorine.



X-ray results showed that the TTF molecule formed crystals in which the double bonds between rings were stacked.²⁶ Also, the chloride salt of the TTF radical cation was found to be a semiconductor with a resistivity of 3.7 ± 1 ohm cm.²⁷ These properties appeared to hold promise that an interesting complex could be formed between the TTF radical cation and the TCNQ radical anion, and the complex can indeed be formed. Early measurements using X-ray photoelectron spectroscopy showed that the degree of charge transfer was 1.0 ± 0.5 electrons per molecule, which would indicate that the complex actually consists of radical cation and radical anion;²⁸ however, more recent measurements indicate that the degree of charge transfer between TTF and TCNQ is only 0.56 ± 0.05 .²⁹ Crystal structures indicate that, as in NMP-TCNQ, the TTF and TCNQ molecules are in alternate stacks.³⁰⁻³²

Coleman *et al.* prepared crystals of TTF-TCNQ complex and reported that exceptionally well-formed, microscopically perfect crystals exhibited extraordinarily high conductivity at 58°K.³³ One such crystal had a conductivity of 1837 (ohm cm)⁻¹ at room temperature. At 58°K, the conductivity vs. temperature curve (Figure 1) appears to be divergent.

For comparison, the conductivity of copper at room temperature is $6 \times 10^5 \text{ (ohm cm)}^{-1}$.

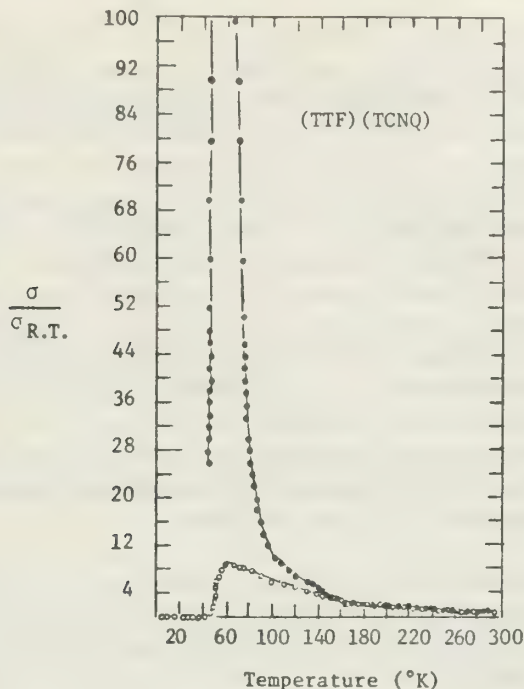


Figure 1. Temperature dependence of the conductivity of (TTF)(TCNQ) single crystal (—●—●—) and of (TTF)(TCNQ) typical crystals (—○—○—).

The Peierls temperature, the temperature at which a compound undergoes a transition from the metallic to the insulating state, is also 58°K. Coleman interpreted the abnormally high conductivity at the Peierls temperature as due to unstable superconducting fluctuations.

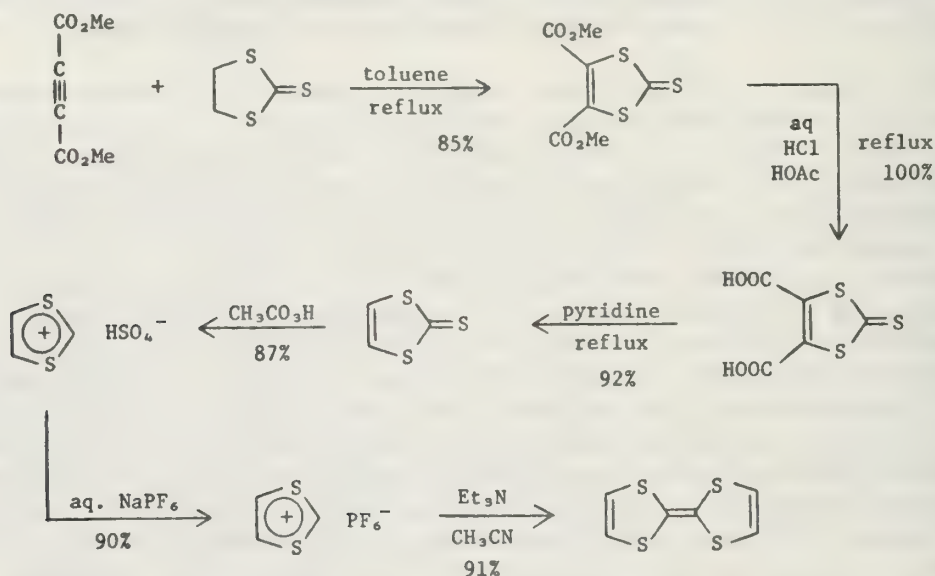
Other researchers have been unable to duplicate Coleman's results.³⁴⁻³⁶ Schafer et al. found that by appropriate placement of the electrical contacts on the crystal it was possible to measure spuriously high currents due to the anisotropic properties of the TTF-TCNQ complex.³⁴ For instance, they were able to obtain spurious room temperature conductivity measurements for TTF-TCNQ of as high as $5000 \text{ (ohm cm)}^{-1}$ as compared to Coleman's maximum of $1837 \text{ (ohm cm)}^{-1}$. Groff et al. reported that their data indicated a maximum conductivity enhancement of 58 times the room temperature conductivity at 58°K.³⁵ In the process of accumulating this data, they discarded all crystals with resistances not reproducible within 2% upon warming and cooling. The earlier paper by Cohen, Coleman, et al., however, had noted that raising and lowering the temperature of the crystal from 50-300°K resulted in gradual crystal deterioration and loss of the extraordinary conductivity maxima reported in Coleman's earlier paper.³⁷ Cohen and Coleman acknowledged Schafer's work in this paper, but challenged his conclusions. They argued that Schafer's method of measuring conductivity inherently underestimates the conductivity of a material, and that their data was qualitatively different from Schafer's spurious data. Furthermore, they argued that their TTF-TCNQ crystals were of very high purity, with gradient sublimation techniques used to purify starting materials, and with reactions and handling of materials carried

out only under inert atmosphere using quartz or Teflon ware. They also stated that crystal perfection was the limiting factor in preparing TTF-TCNQ of high conductivity.

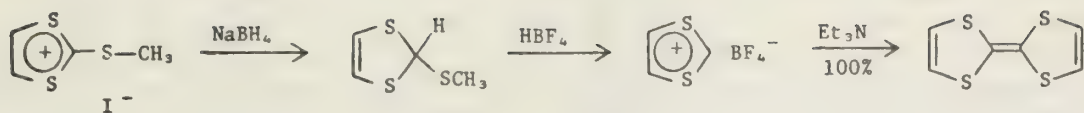
Gemmer et al. later did a study on the relative merit of the techniques of recrystallization, sublimation, and gradient sublimation in the purification of TTF and TCNQ for use in the preparation of the TTF-TCNQ complex through the use of HPLC and UV spectroscopy.³⁸ They found that samples purified by any of the three methods showed no detectable contamination except for a trace of acetonitrile in TCNQ recrystallized from that solvent. In an attempt to ascertain the effects of impurities on the TTF-TCNQ complex, some crystals were prepared under carefully controlled conditions using Teflon ware into which a small quantity of NaCl had been introduced in order to simulate salts which might be leached out of glassware during the course of the reaction. They found that one exceptionally well-formed crystal prepared in this manner exhibited a conductivity maximum at 59°K of 7.2×10^4 (ohm cm)⁻¹, 120 times the room temperature conductivity of the crystal. However, voltage monitoring using the methods of Schafer indicated that this was due to inhomogeneous currents in the crystal.

Bickford and Kanazawa later did extensive work on the attachment of silver paint electrodes to TTF-TCNQ crystals and found that the mode of attachment of the electrode is very important in the determination of conductivity in such systems.³⁹

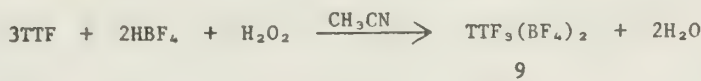
Since the method of preparation of TTF-TCNQ complex as well as that of TTF and TCNQ themselves has been the subject of such intense scrutiny, it is not surprising to find that a number of synthetic methods have been devised for the synthesis of these compounds and their analogs. Melby et al. synthesized TTF via the following route:^{40,41}



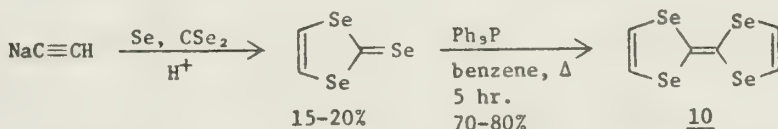
Wudl et al. devised the following synthesis for TTF; however, they recommended Melby's synthesis for the preparation of large amounts of the product:⁴²



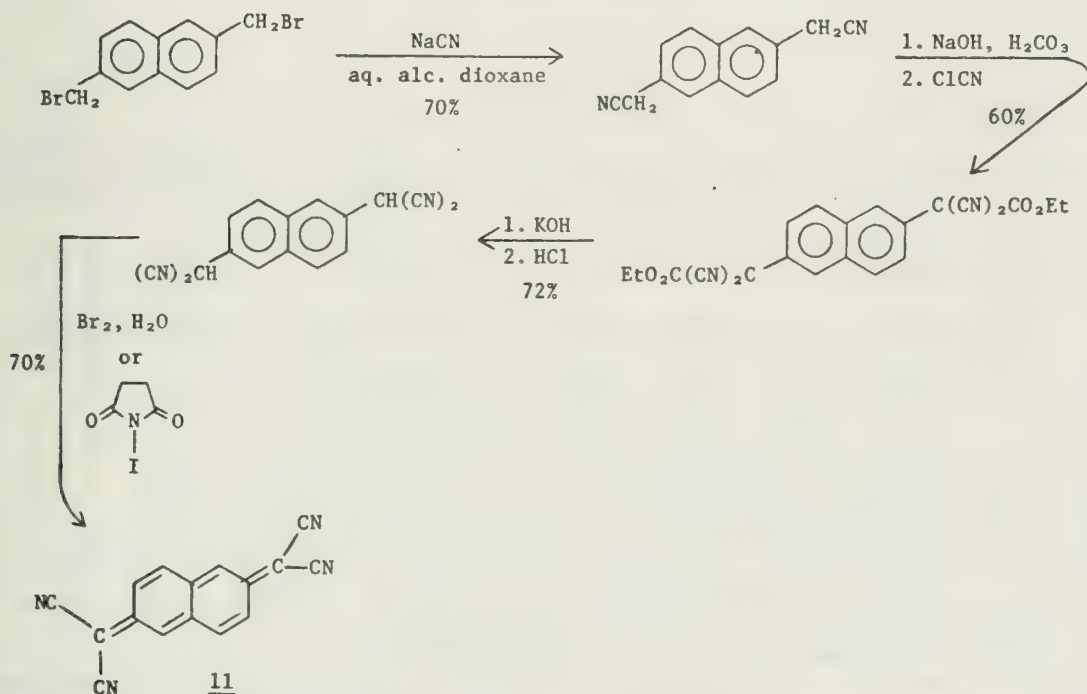
Wudl also synthesized $\text{TTF}_3(\text{BF}_4)_2$ (9) as a reagent for use in the preparation of other TTF salts.⁴³



Engler and Patel prepared the selenium analog of TTF, tetraseleno-fulvalene (TSF, 10), as follows.⁴⁴



Analogues to TCNQ have been prepared. One such analog, synthesized by Sandman and Garito, is the 2,6-tetracyanoquinodimethane derivative of naphthalene, TNAP (11).⁴⁵



A number of substituted TTF, TSF, and TCNQ's have also been prepared.⁴⁶

4. Biological Superconductors. Some of the more speculative thought on the subject of organic superconductors is concerned with the possibility that small superconductive regions exist within biological polymers such as DNA and RNA or in microscopic aggregations of molecules such as cholesterol.

Cope suggested that single-electron tunneling between superconductive regions might be the rate-limiting factor in various nerve and growth processes.⁴⁷ The rate should then increase as the temperature increases, and a plot of the energy of activation for these processes vs. temperature should exhibit a region of linearity that can be extrapolated to the system's critical temperature, T_C , as is found for a number of biological systems involving the transmission of nerve impulses and growth processes where T_C ranges from 23.4-41.5°C. This may explain the adverse effect that strong magnetic fields have on growth.⁴⁸ Cope further suggests that microscopic superconductive regions exhibiting Josephson (two-electron) tunneling across thin insulating layers which can be affected by weak magnetic fields may be responsible for the ability of organisms to detect such fields.^{8,49}

Halpern and Wolf and Halpern^{50a-d} reported that the sodium salts of cholic, desoxycholic, lithocholic, and cholanic acids appear to contain small superconducting domains within an insulating matrix with transition temperatures of 30, 60, 130, and 277°K, respectively. Superconductivity was inferred from a large resistance decrease and strong diamagnetic properties below the observed transition temperature. Goldfein reported that the X-ray structure for lithocholic acid showed no lattice changes for samples above 25°C or below the critical temperature of 130°K, consistent with the assumption of superconductivity.^{50a} Goldfein also obtained a linear plot for $\ln(T_C)$ vs. e/a where e/a is equal to the average number of valence electrons for each atom in the compound, similar to plots for superconducting alloys of transition metals. Extrapolation of this line indicates that cholesterol could be superconducting at temperatures as high as 920°K.

BIBLIOGRAPHY

1. H. K. Onnes, Commun. Phys. Lab. Univ. Leiden, no. 119b (1911), quoted in D. Shoenberg, "Superconductivity", Cambridge University Press, 1951, p. 1.
2. V. L. Ginzburg and L. D. Landau, Zh. Eksperim. i Teor. Fiz., 20, 1064 (1950).
3. J. Bardeen, L. N. Cooper, and J. R. Schrieffer, Phys. Rev., 108, 1175 (1957).
4. L. N. Cooper, Phys. Rev., 104, 1189 (1956).
5. W. A. Little, Phys. Rev., 134, A1416 (1964).
6. W. A. Little, Sci. Amer., 212 (2), 21 (1965).
7. W. A. Little, J. Polymer Sci., C, 29, 133 (1970).
8. B. D. Josephson, Rev. Mod. Phys., 36, 216 (1964).
9. J. H. Hodgkin and J. Heller, J. Polymer Sci., C, 29, 37 (1970).
10. R. S. Schneider, J. Polymer Sci., C, 29, 27 (1970).
11. J. H. Hodgkin, Proc. Roy. Aust. Chem. Inst., 40, 50 (1973).
12. K. F. G. Paulus, Mol. Phys., 10, 381 (1966).
13. P. M. Chaikin, A. F. Garito, and A. J. Heeger, Phys. Rev., B5, 4966 (1972).
14. P. M. Chaikin, A. F. Garito, and A. J. Heeger, J. Chem. Phys., 58, 2336 (1973).
15. D. S. Acker, R. J. Harder, W. R. Hertler, W. Mahler, L. R. Melby, R. E. Benson, and W. E. Mochel, J. Am. Chem. Soc., 82, 6408 (1960).
16. D. S. Acker and W. R. Hertler, J. Am. Chem. Soc., 84, 3370 (1962).
17. J. Kommandeur and F. R. Hall, Bull. Am. Phys. Soc., Series II, 4, 421 (1959).

18. L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *J. Am. Chem. Soc.*, 84, 3374 (1962).
19. L. R. Melby, *Can. J. Chem.*, 43, 1448 (1965).
20. C. J. Fritchie, Jr., *Acta Cryst.*, 20, 892 (1966).
21. A. J. Epstein, S. Etemad, A. F. Garito, and A. J. Heeger, *Phys. Rev.*, B5, 952 (1972).
22. S. Hiroma, H. Kuroda, and H. Akamata, *Bull. Chem. Soc. Jpn.*, 44, 9 (1971).
23. F. Wudl, G. M. Smith, and E. J. Hufnagel, *Chem. Commun.*, 1453 (1970).
24. R. Mayer and B. Gebhardt, *Chem. Ber.*, 97, 1298 (1964).
25. E. Klingsberg, *J. Am. Chem. Soc.*, 86, 5290 (1964).
26. W. F. Cooper, N. C. Kenny, J. W. Edmond, A. Nagel, F. Wudl, and P. Coppens, *Chem. Commun.*, 889 (1971).
27. F. Wudl, D. Wobschall, and E. J. Hufnagel, *J. Am. Chem. Soc.*, 94, 670 (1972).
28. M. A. Butler, J. P. Ferraris, A. N. Block, and D. O. Cowan, *Chem. Phys. Lett.*, 24, 600 (1974).
29. I. Ikemuto, T. Sugano, and H. Kuroda, *Chem. Phys. Lett.*, 49, 45 (1977).
30. T. J. Kistenmacher, T. E. Phillips, and D. O. Cowan, *Acta Cryst. B*, 30, 763 (1974).
31. R. H. Blessing and P. Coppens, *Solid State Commun.*, 15, 215 (1974).
32. A. J. Schultz, G. D. Stucky, R. H. Blessing, and P. Coppens, *J. Am. Chem. Soc.*, 98, 3194 (1976).
33. L. B. Coleman, M. F. Cohen, D. J. Sandman, F. G. Yamagishi, A. F. Garito, and A. J. Heeger, *Solid State Commun.*, 12, 1125 (1973).
34. D. Schafer, F. Wudl, G. A. Thomas, J. P. Ferraris, and D. O. Cowan, *Solid State Commun.*, 14, 347 (1974).
35. R. P. Groff, A. Suna, and R. E. Merrifield, *Phys. Rev. Lett.*, 33, 418 (1974).
36. T. Ishiguro, S. Kagoshima, and H. Anzai, *J. Phys. Soc. Jpn.*, 41, 351 (1976).
37. M. J. Cohen, L. B. Coleman, A. F. Garito, and A. J. Heeger, *Phys. Rev.*, B10, 1298 (1974).
38. R. V. Gemmer, D. O. Cowan, T. O. Poehler, A. N. Block, R. E. Pyle, and R. H. Banks, *J. Org. Chem.*, 40, 3544 (1975).
39. L. R. Bickford and K. K. Kanazawa, *J. Phys. Chem. Solids*, 37, 839 (1976).
40. L. R. Melby, H. D. Hartzler, and W. A. Sheppard, *J. Org. Chem.*, 39, 2456 (1974).
41. B. R. O'Connor and F. N. Jones, *J. Org. Chem.*, 35, 2002 (1970).
42. F. Wudl, M. L. Kaplan, E. J. Hufnagel, and E. W. Southwick, Jr., *J. Org. Chem.*, 39, 3608 (1974).
43. F. Wudl, *J. Am. Chem. Soc.*, 97, 1962 (1975).
44. E. M. Engler and V. V. Patel, *J. Am. Chem. Soc.*, 96, 7376 (1974).
45. D. J. Sandman and A. F. Garito, *J. Org. Chem.*, 39, 1165 (1974).
46. G. D. Stucky, A. J. Schultz, and J. M. Williams, *Ann. Rev. Mater. Sci.*, 7, 301 (1977).
47. F. W. Cope, *Physiol. Chem. Phys.*, 3, 403 (1971).
48. M. R. Pereira, L. G. Nutini, J. C. Fardon, and E. S. Cook, *Proc. Soc. Exp. Biol. Med.*, 124, 573 (1967).
49. F. W. Cope, *Physiol. Chem. Phys.*, 5, 173 (1973).
50. (a) S. Goldfein, *Physiol. Chem. Phys.*, 6, 261 (1974); (b) E. H. Halpern and A. A. Wolf, "Cryogenic Engineering", Vol. 17, K. D. Timmerhaus, ed., Plenum Press, 1972, p. 109, quoted in S. Goldfein, ref. 50a; (c) E. H. Halpern, "High Temperature, Nonmetallic Superconductors", Naval Ship R & D Center, Annapolis, Maryland, 1973, Report #3917, quoted in S. Goldfein, ref. 50a; (d) E. H. Halpern, unpublished results, quoted in S. Goldfein, ref. 50a.

ORGANIC SYSTEMS AS MODELS FOR α -CHYMOTRYPSIN

Reported by Anthony W. Czarnik

November 21, 1978

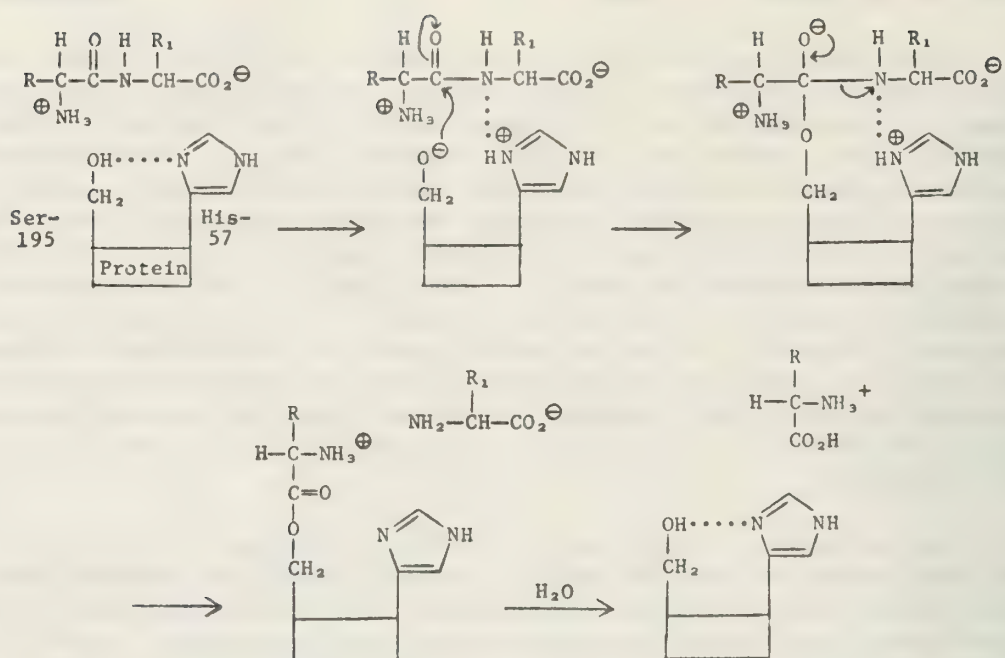
Enzyme modeling has, within the past ten or fifteen years, become a major research area in bioorganic chemistry. Attempts to mimic the essential characteristics of enzymes, such as the binding of substrate molecules, the stereospecificity of interactions, and the enhancement of reaction rates have been carried out successfully in many cases. A variety of approaches have been used involving organic systems, including spatially unconstrained catalytic groups, spatially constrained catalytic groups, water-soluble polymers,^{1a-c} micelles,^{1d,e} and macrocycles.^{1d-f} In addition, the use of inorganic systems^{1g,h} and of computer simulation¹ⁱ have been reported. As in any model study, the objective of enzyme modeling is to gain understanding of a complex system by dissecting a proposed mechanism into simpler processes, then testing each process to see if, collectively, they can in fact account for the observed properties of the system.

The collection of enzymes for which mechanisms of substantial detail have been proposed is quite small, consisting only of chymotrypsin, lysozyme, carboxypeptidase, and possibly some dehydrogenases. Of these, chymotrypsin has to date been most extensively modeled. In this abstract the organic systems which have been investigated as models for α -chymotrypsin will be examined and their proposed relevance to the enzyme discussed.

Requisite to the modeling of an enzyme is a detailed knowledge of its interactions with substrate molecules. The three-dimensional structure of α -chymotrypsin and of its active site have been well documented both by chemical studies with model substrates² and by X-ray diffraction analysis.^{3a-c} The enzyme consists of three chains designated as A, B, and C, and derives a considerable degree of its tertiary structure from five disulfide bridges. The catalytic groups at the active site are located on the B and C chains; these groups are generally considered to be a histidine residue on the B chain (labeled His-57) and a serine residue on the C chain (labeled Ser-195).⁴ That these groups are in fact active in catalysis has been directly shown by inactivation of the enzyme upon exposure to functional group specific reagents¹⁹ and indirectly by kinetic studies at various pH's.^{4b} These histidine and serine residues have been shown to lie in close proximity to each other⁵ and to an aspartic acid residue (labeled Asp-102) which is thought by some investigators to be involved in the catalytic activity of the enzyme.⁶

The search for the mechanism of hydrolytic action by α -chymotrypsin on various natural and synthetic substrates has persisted for several decades and has proven to be a classic example of the application of the scientific method to a biochemical problem. While a number of theories have been put forth,^{4b} only a few can successfully explain the large amount of data now compiled about the structure and function of the enzyme. The most widely accepted mechanism¹¹ is that illustrated in Figure 1. In this proposed mechanism, the substrate molecule initially binds at the active site through a combination of hydrogen bonding, dipole-dipole interactions, and hydrophobic interactions which cause the peptide (or ester) bond to be oriented near the catalytic groups. Ser-195, deprotonated by the adjacent His-57, affects a nucleophilic attack on the carbonyl group and releases the nitrogen end of the peptide bond

Figure 1

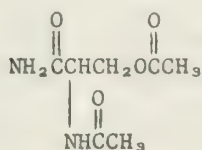


as the first product, leaving an acylated enzyme intermediate. Then, water, acting as a nucleophile, displaces the aminoacyl group from the enzyme with the participation of the now deprotonated imidazole group, and the second product of the hydrolysis is released from the active site. Evidence for this two-step mechanism has been compiled from a number of sources, including the isolation and even recrystallization of some aminoacyl enzymes.⁷

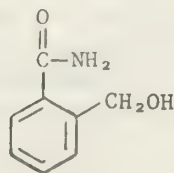
Spatially Unconstrained Catalytic Groups. The action of imidazole as a general base catalyst in the hydrolysis of activated esters has been studied by Jencks⁹ and by Bruice.¹⁰ Similarly, Hardman and co-workers¹² have evaluated imidazole catalysts of the hydrolysis of N,O-diacetylserinamide (1) as a model for the deacylation of aminoacyl- α -chymotrypsins. They calculated the activation parameters for this reaction and found a reduction in the ΔE^\ddagger of at least $7.4 \text{ kcal} \cdot \text{mol}^{-1}$ relative to $20.8 \text{ kcal} \cdot \text{mol}^{-1}$ for the uncatalyzed hydrolysis. The rate of reaction was not greatly enhanced because of an unfavorable change in the ΔS^\ddagger of about $(-)35.8 \text{ cal} \cdot ^\circ\text{K}^{-1} \cdot \text{mol}^{-1}$; however, the authors concluded that as the entropy change for the deacylation of aminoacyl- α -chymotrypsins has been observed to be substantially less than this value ($\Delta S^\ddagger = (-)21.3 \text{ cal} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$), imidazole catalysis could accelerate the rate of reaction by 10,000 fold.

Another study which investigated the feasibility of imidazole-facilitated displacement on an amide was performed by Shafer and co-workers.²⁰ The kinetics of lactonization of 2-hydroxymethylbenzamide (2) and of its N-benzyl derivative were determined at various concentrations of imidazole buffer solution and the apparent second-order rate constant found to be $4.5 \times 10^{-3} \text{ min}^{-1} \cdot \text{M}^{-1}$ at 25°C . The authors reported that imidazole was clearly more efficient in catalyzing cyclization of the hydroxyamides than imidazolium ion; in fact, in comparison to specific base catalysis, they observed the second-order rate constant for imidazole-catalyzed lactonization, assuming a properly oriented unionized hydroxyl

group is present, to be approximately seven times that of hydroxide ion catalyzed hydrolysis of benzamide.

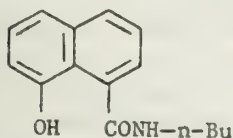


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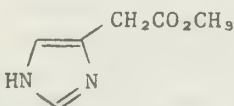


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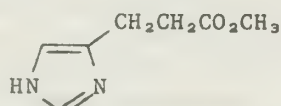
Spatially Constrained Catalytic Groups. In an attempt to test the validity of one step in the proposed mechanism, that of nucleophilic attack on the peptide bond by a deprotonated serine residue, Menger and Brock⁸ studied the hydrolytic properties of N-n-butyl-8-hydroxy-1-naphthoamide (3) under conditions in which the naphthol is largely ionized. They reasoned that since the naphtholate anion was rigidly held in close proximity to the amide, it should act as a general base and assist rapid hydrolysis of the amide; however, after 48h at 25°C and pH 11.48, less than 5% of the starting material had disappeared. Consequently, they argued that, if monofunctional general acid-general base catalysis is the sole source of rate acceleration in α -chymotrypsin, then the overall rate of hydrolysis of 3 should be of the same order of magnitude as that of the enzyme. The rates were found to differ by a minimum of 10^5 , and on the basis of this evidence they postulated that at least a second catalytic functionality must be present at the enzyme's active site.



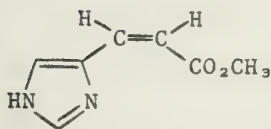
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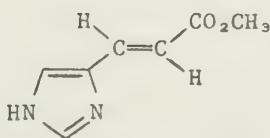
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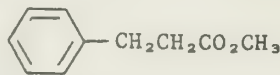
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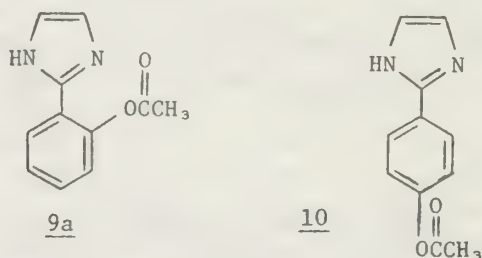
While significant general base catalysis by imidazole of unsubstituted alkyl esters has not been reported,^{10b,13} Jencks has observed the existence of a slight general base catalysis of methyl acetate at high imidazole concentrations.¹⁴ Therefore, approximation of a substrate and imidazole in an active site, which would be expected to increase the "local" concentration of the catalytic group drastically, might be expected to result in a substantial contribution of this form of catalysis to the overall rate enhancement. Such a theory has been tested by several investigators utilizing model compounds with catalytic groups spatially constrained to the vicinity of the substrate bond. One such study was carried out by Koshland and co-workers¹⁵ in which the rates of hydrolysis for a series of substituted esters were measured (Table 1). It is important to note that the rates of hydrolysis for 7 and 8 are essentially proportional to the hydroxide concentration, while 4, 5, and 6 each show rate enhancements of 3 to 8-fold at pH 7 as compared to 7 and 8. That

Table 1. Rates of Hydrolysis of Some Spatially Constrained Substituted Esters¹⁵

<u>Compound</u>	10•k in s ⁻¹ at 105°C		
	<u>pH 6.0</u>	<u>pH 7.0</u>	<u>ph 8.5</u>
<u>4</u>	0.030	0.170	1.36
<u>5</u>	0.011	0.064	0.72
<u>6</u>	0.039	0.14	1.00
<u>7</u>	0.0019	0.022	0.69
<u>8</u>	0.0028	0.028	0.94

this catalytic effect is intramolecular was shown by experiments at 0.005, 0.010, and 0.015 M concentrations of ester which show the rate constants to be unchanged. A similar study was done by Utaka¹⁶ in which the hydrolysis rate constants were determined from related model compounds in which internal rotations of the esters were frozen, a circumstance which would be expected to exist in the active site of α -chymotrypsin. He found that the rate increased by factors as high as 11.5 over the rotationally unrestricted ester as the degree of spatial constraint was increased.

Rogers and Bruice¹⁷ have examined the rate data for another series of spatially constrained enzyme models, the o- and p- imidazolylacetyl-phenolates (9a and 10). Their findings implicate general acid assistance to H₂O attack of the o- disubstituted compound at low pH (2-4) by the neighboring imidazolium cation. At neutral pH general base catalysis by imidazole was observed, and at alkaline pH (9-11) evidence was obtained to support intramolecular acetyl group transfer to the imidazolyl anion with subsequent hydrolysis of the acetylimidazole intermediate. This would seem to support general base catalysis by imidazole in α -chymotrypsin as maximal activity of the enzyme is found near pH 8.



An interesting application of these two classes of enzyme model systems to the establishment of hypothetical enzyme mechanisms is found in recent studies concerning the proposed "charge-relay" system of the serine esterases. This hypothesis, formulated by Hartley and co-workers,⁶ states that an ionized carboxylic acid residue within hydrogen bonding distance of His-57 functions as a second general base in concert with the histidine imidazolyl group to facilitate the acylation and deacylation steps for ester hydrolysis. Precedent for such a tandem general base mechanism does exist in the literature.²¹ Using spatially unconstrained catalytic groups, Khurgin and Filatova²² have reported spectroscopic data purportedly indicating the existence of such a charge-relay system in aqueous solutions of imidazole and p-nitrophenol. Several weaknesses exist in the work,

however, including the lack of a convincing demonstration that changes in the absorption spectrum of the phenolate ion upon an increase in imidazole concentration definitively arise from formation of a ternary complex and are not due to other interactions. Also, while the authors implicate the formation of an undissociated ion pair between 3-(2-furyl)acrylic acid and imidazole in DMSO solution, no evidence is presented for the existence of a system including acid, imidazole, and alcohol groups as required to model the proposed charge-relay system in α -chymotrypsin.

Another series of experiments testing this hypothesis has been carried out by Rogers and Bruice²³ in which the rates of hydrolysis for several spatially constrained phenyl esters were examined as shown in Table 2. It was observed that rate enhancement upon the introduction of a hydrogen bonded carboxylate was only threefold, a negligible increase from the standpoint of enzymatic catalysis. In order to better approximate the hydrophobic environment of the enzyme's active site, the hydrolyses were also carried out in acetonitrile containing 3.3 M H₂O. The investigators found that transferring from H₂O to a solvent of limited H₂O concentration had virtually no effect on the catalytic role of the carboxylate group in the intermolecular reactions.

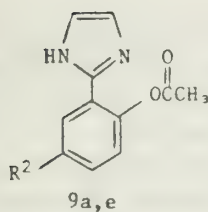
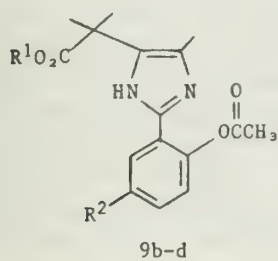
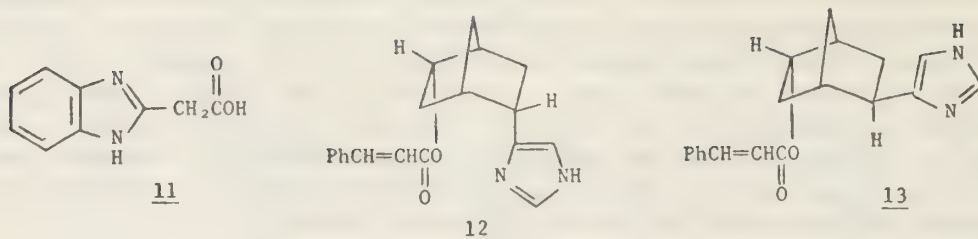


Table 2. Rates of Hydrolysis for Some Model Compounds of the "Charge-Relay" System²³

Compound	R ¹	R ²	k(min ⁻¹)
<u>9a</u>	-	H	1.00 x 10 ⁻²
<u>9b</u>	H	H	2.75 x 10 ⁻²
<u>9c</u>	CH ₃	H	9.50 x 10 ⁻³
<u>9d</u>	H	SO ₃ [⊖]	3.60 x 10 ⁻²
<u>9e</u>	-	SO ₃ [⊖]	1.20 x 10 ⁻²

Bender and co-workers have, on the other hand, provided evidence which seems to support the importance of the charge-relay system. In one investigation,⁴³ they found an 8-fold acceleration due to cooperation of the hydroxyl, imidazolyl, and carboxyl groups in the general base catalyzed hydrolysis of ethyl chloroacetate by 2-benzimidazole acetic acid (11), which has both the imidazolyl and carboxyl groups in the same molecule.

In another investigation, Utaka, Takeda, and Bender¹⁸ reported the synthesis of endo- and exo-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-endo-2-yl trans-cinnamates (12 and 13) as potential enzyme models. More recently,⁴⁴ they reported that 12 functions as an intramolecular general base catalyst, and, furthermore,³⁶ that the rate acceleration attained at a benzoate anion concentration of 0.5 M was 2500 times that attained at zero benzoate concentration. No intramolecular activity was found for 13.



Water-Soluble Polymers. This class of enzyme models mimics two properties which enzymes exhibit: binding and enhancement of reaction rates. While numerous attempts have been made to prepare synthetic polymers with the catalytic activity of hydrolytic enzymes,²⁴ most do not act upon small uncharged molecules and are therefore not useful as models for α -chymotrypsin.

There appears to be only one class of water-soluble synthetic polymers which has been found to be useful in modeling α -chymotrypsin: the polyethyleneimines (PEI). Klotz,²⁵ in 1968, reported that PEI-6 (average molecular weight 600), after acylation of approximately 10% of its residues with lauroyl chloride, bound a small, uncharged molecule, dimethylaminoazobenzene, with an affinity greater than that of even serum albumin. The next year, Klotz²⁶ reported that this same derivative enhanced the rates of cleavage of three nitrophenol esters as compared to a reference amine, propyl amine. It was concluded that this enhancement was due to the presence of apolar binding sites situated in proximity to amine residues of the polymer. As expected, the degree of rate enhancement increased with increasingly large apolar substituents on the esters as seen: p-nitrophenyl acetate, 17-fold; p-nitrophenyl caproate, 135-fold; p-nitrophenyl laurate, 13,100-fold.

A further improvement of the PEI "synzymes" was realized when catalytic groups were introduced into the polymer. Klotz, Royer, and Scarpa²⁷ have reported that PEI-600 derivatized with 10% dodecyl groups and 15% methyleneimidazole groups had catalytic activity 27% that of α -chymotrypsin itself towards the hydrolysis of nitrophenyl esters, while PEI-600 derivatized with 8% $-\text{CH}_2\text{CON}(\text{OH})\text{CH}_3$, 8% lauroyl groups, and 6.6% 4-(carboxymethylene)imidazole had 31% of the reference activity. In addition, the kinetics of these reactions were consistent with the mechanism proposed for α -chymotrypsin: pre-equilibrium binding, fast acylation, slow deacylation.

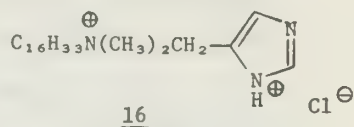
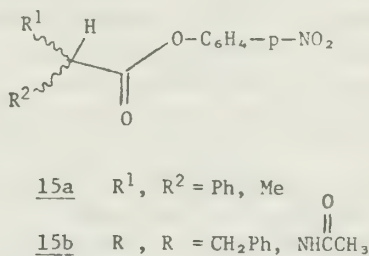
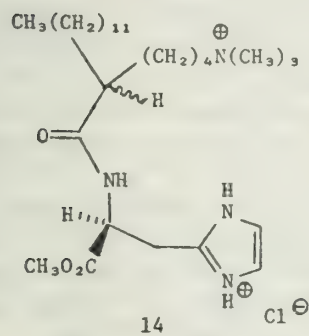
Additional studies have been carried out concerning the binding ability of benzylated polyethyleneimines in aqueous solutions²⁸ and the change in pK_a values for the amino groups located at the hydrophobic regions of alkylated PEI derivatives.²⁹

Micelles. A number of functionalized surfactants have been studied with respect to the hydrolysis of phenyl esters. Rate enhancements are generally attributed to the approximation of catalytic and functional groups upon being placed into a hydrophobic environment. One example of micelle-promoted ester hydrolysis was reported by Brown and Bunton⁴⁰ in which the chiral surfactant 14, at concentrations of zero to $6 \times 10^{-3} \text{ M}$, was allowed to interact with enantiomeric substrates (15). Rate enhancements for hydrolysis of 283-fold were observed, and, while the binding efficiencies of each enantiomer were nearly identical, the rate constants

demonstrated an enantiomeric specificity of as large as 3.05 towards the S-(+)- isomer.

Other micellar systems utilize non-covalently associated bifunctionalities in their mechanisms of catalysis. Tabushi and co-workers⁴¹ report that N-methyl-N-lauroylhydroxamic acid, when used in a CTAB micelle, displayed a very large catalytic activity towards the hydrolysis of p-nitrophenyl acetate, close even to the activity of α -chymotrypsin itself. They observed Michaelis-Menton kinetics for the system and calculated a rate enhancement of 333 for the bifunctional catalysis as compared to the greatest enhancement afforded by either component alone. The enhanced catalytic effect of the hydrophobic hydroxamate was ascribed to the increased nucleophilicity of the hydroxamate anion in the unsolvated, yet still polar atmosphere of the micelle. Such a mechanism is proposed to account similarly for the abnormally high nucleophilicity of Ser-195 in the enzyme itself.

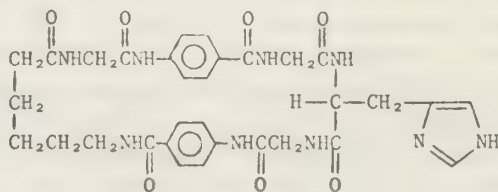
Another example of a bifunctional micellular enzyme model was presented by Sunamoto and co-workers⁴² in 1975. They investigated the use of aqueous micelles composed of the substituted imidazole 16 in conjunction with the macrocyclic oxime 19 previously tested in an attempt to affect greater activity towards the hydrolysis of three p-nitrophenyl carboxylates. They found that the cooperative catalysis was greater than that of the individual components by factors ranging from 2.4 to 38.5, depending on the ester. As opposed to the mechanism of α -chymotrypsin action, however, Sunamoto ascribes the activity of this system to the formation of a ternary complex between micelle, ester and macrocycle followed by transient acyl transfer to the imidazole before a final transfer to the hydroxamate.



Macrocycles. The use of macrocyclic compounds as enzyme models revolves around the idea that binding of a substrate molecule, either by hydrophobic interactions or through the use of specific functional groups, to the interior cavity of the macrocycle can be accomplished and that, through proper functionalization within this binding "pocket", catalysis may be carried out in a way similar to that of the enzyme.

One class of macrocycles which has been investigated is the synthetic cyclic peptides. Kopple³⁰ and Sheenan³¹ have studied their potential use as general enzyme models; however, only the system reported by Roeske and co-workers³² appeared to be a potential model for chymotrypsin. They proposed that the cyclic heptapeptide 17 should provide a relatively apolar cavity as binding site and that the peptide bridges between the p-amino-benzoyl residues would allow for the placement of functional side chains which could then serve as a catalytic site. Unfortunately, this compound

has a very low solubility (2×10^{-6} M) in neutral and basic aqueous solutions which precluded a detailed study of its interaction with substrates. Its activity in catalyzing the hydrolysis of 2,4-dinitrophenyl acetate was examined and found to be less than even that of unsubstituted imidazole alone.



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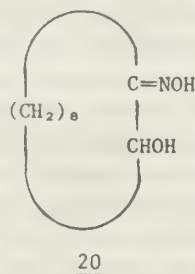
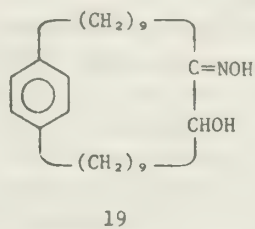
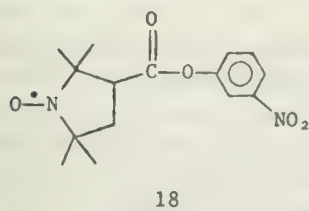
Perhaps the class of enzyme models which mimics the largest number of enzymic characteristics is the cycloamyloses, α -1,4-linked D-glucose macrocyclic polymers. In 1967, Bender and co-workers³⁴ published their results concerning the activity of cyclohexa-, hepta-, and octaamylose towards the hydrolysis of a number of phenyl esters. The observed hydrolysis rates clearly showed all m-substituted compounds to have increased reaction rates as compared to those of the p-substituted analogues. In addition, the hydrolyses were found to be pseudo-first order and showed saturation kinetics. The high degree of specificity seen in the reaction of substrates with cyclohexaamylose is attributed to the positioning of the ester group with respect to secondary hydroxyl groups on the periphery of the macrocycle.

Cramer and Mackensen³³ have reported that the attachment of an imidazole residue to β -cycloamylose (β -cyclodextrin) resulted in a model compound with greater activity towards the hydrolysis of p-nitrophenyl acetate than either the cyclodextrin itself or a co-solution of cyclodextrin and imidazole. They found that a maximal increase (2.4 times greater than co-solution) was observed when the hydroxymethylimidazole derivative was used with two imidazole groups per cyclodextrin molecule.

In 1975, Hattori and co-workers,³⁵ in an attempt to improve upon the relatively small rate enhancement observed by Cramer and Mackensen³³ with their imidazole-cyclodextrin model, synthesized an α -cyclodextrin histamine compound in which the catalytic histamine ($-\text{NHCH}_2\text{CH}_2\text{-Im}$) group is attached to a secondary alcohol group on the more open face of the torroidal α -cyclodextrin. This is in contrast to attachment to a primary alcohol group at C-6 of a glucose unit which is located on the essentially closed face of the cyclodextrin molecule. Kinetic results show a pseudo-first order rate constant for the cyclodextrin-histamine catalyzed hydrolysis 6.9 times larger than that of a co-solution of the individual components. Competitive inhibition and substrate specificity were also observed in this system.

In addition to the many similarities between enzymes and the cyclodextrin series noted by other workers, Kaiser³⁷ has observed a very high enantionmeric specificity in the reaction of cyclohexaamylose with racemic 3-carboxy-2,2,5,5-tetramethylpyrrolidin-1-oxy m-nitrophenyl ester (18), a substrate containing an asymmetric carbon adjacent to the carbonyl group of the hydrolytically labile ester function. A partial hydrolysis of racemic 18 by cyclohexaamylose gave the expected (-)-18 species as the unchanged ester.

Sunamoto³⁸ has recently investigated the use of oximes 19 and 20 as model systems in the deacylation of p-nitrophenyl carboxylates. While 19 showed catalytic activity towards the hydrolysis of p-nitrophenyl decanoate and laurate, it did not show significant activity towards the corresponding acetate or hexanoate, while oxime 20 and acetoxime showed no effect on any of the substrates tested. Also, binding constants were calculated and saturation kinetics observed which further substantiate Sunamoto's explanation that the incorporation of substrate into the binding pocket plays a critical role in the oxime's catalytic effectiveness. Further studies into the kinetic and thermodynamic parameters of this system have been made.³⁹



In summary, the application of organic systems as models for α -chymotrypsin has reinforced the belief that the unique properties of enzymes can be understood in terms of more fundamental physical organic concepts already well established. However, while the rate acceleration achieved by the enzyme has been essentially attained in model systems for a few substrates, the scope of its catalytic ability has not. Furthermore, the relative importance of individual modes of catalysis and of their interplay at the active site is only now beginning to be investigated. Therefore, further work in this area should provide new insights into the mechanism of α -chymotrypsin and, more importantly, towards the understanding of biological catalysis in general.

BIBLIOGRAPHY

1. For reviews see: (a) W. Saenger, Jerusalem Symp. Quantum Chem. Biochem., 1975 (pub. 1976), 8, 265; (b) I. Tabushi, Yuki Gosei Kagaku Kyokai Shi 1974, 32(10), 819; (c) O. Mikes, J. Veprek-Siska, and P. Strop, Chem. Listy, 70, 125 (1976); (d) I. S. Scarpa, H. C. Kiefer, and I. M. Klotz, Inta. Sci. Chem. Rep., 8, 45 (1974); (e) P. Strop and J. Zachoval, Sb. Vys. Sk. Chem.-Technol. Praze., Org. Chem. Technol. 1975, C22, 7; (f) M. Hatano, M. Yoneyama, and Y. Nozawa, Kogyo Kagaku Zasshi, 72, 431 (1969); (g) T. Higashiyama and A. Nakahara, Kagaku No Ryoiki, Zokan 1970, (90), 179; (h) R. Breslow, Advan. Chem. Ser. 1971, No. 100, 21-43; (i) J. A. Burns, Quant. Biol. Metab. Int. Symp., 3rd, 1967, 75-80.
2. T. N. Pattabiraman and W. B. Lawson, J. Biol. Chem., 247, 3029 (1971).
3. (a) T. A. Steitz, R. Henderson, and D. M. Blow, J. Mol. Biol., 46, 337 (1969); (b) P. B. Sigler, D. M. Blow, B. W. Matthews, and R. Henderson, J. Mol. Biol., 35, 143 (1968); (c) D. M. Blow, Biochem. J., 112, 261 (1969).
4. (a) A. Lehninger, "Biochemistry", Worth, New York, 1975, pp. 217-231; (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, 1969, pp. 45-59, 218-226.
5. B. W. Matthews, P. B. Sigler, R. Henderson, and D. M. Blow, Nature, 214, 652 (1967).
6. D. M. Blow, J. J. Birktoff, and B. S. Hartley, Nature, 221, 337 (1969).

7. C. E. McDonald and A. K. Balls, *J. Biol. Chem.*, 227, 727 (1957).
8. F. M. Menger and H. T. Brock, *Tetrahedron*, 24, 3453 (1968).
9. (a) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 234, 1272 (1959);
(b) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 83, 1743 (1961).
10. (a) U. K. Pandet and T. C. Bruice, *J. Am. Chem. Soc.*, 82, 3386 (1960)
(b) T. C. Bruice and S. J. Benkovic, *ibid.*, 85, 1 (1963).
11. M. L. Bender and F. J. Kezdy, *Annu. Rev. Biochem.*, 34, 49 (1965).
12. M. J. Boland, M. J. Hardman, and I. D. Watson, *Bioorg. Chem.*, 3, 213 (1974).
13. T. C. Bruice, *Brookhaven Symp. Biol.*, 15, 52 (1962).
14. J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 86, 837 (1964).
15. A. Lukton, D. Blackman, and D. E. Koshland, Jr., *Biochim. Biophys. Acta*, 85, 512 (1964).
16. M. Utaka, J. Koyama, and A. Takeda, *J. Am. Chem. Soc.*, 98, 984 (1976).
17. G. A. Rogers and T. C. Bruice, *ibid.*, 96, 2463 (1974).
18. M. Utaka, A. Takeda, and M. L. Bender, *J. Org. Chem.*, 39, 3772 (1974).
19. Y. Nakagawa and M. L. Bender, *J. Am. Chem. Soc.*, 91, 1566 (1969).
20. C. J. Belke, S. C. K. Su, and J. A. Shafer, *ibid.*, 93, 4552 (1971).
21. T. C. Bruice and S. J. Benkovic, *ibid.*, 86, 418 (1964).
22. Y. I. Khurgin and T. N. Filatova, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 10, 2315 (1973).
23. G. A. Rogers and T. C. Bruice, *J. Am. Chem. Soc.*, 96, 2473 (1974).
24. References #1-6 in ref. 27.
25. I. M. Klotz and A. R. Sloniewsky, *Biochem. Biophys. Res. Comm.*, 31, 421 (1968).
26. G. P. Royer and I. M. Klotz, *J. Am. Chem. Soc.*, 91, 5885 (1969).
27. I. M. Klotz, G. P. Royer, and I. S. Scarpa, *Proc. Nat. Acad. Sci.*, 68, 263 (1971).
28. V. S. Pshezhetskii, G. A. Murtazaeva, and V. A. Kabanov, *Eur. Poly. J.*, 10, 581 (1974).
29. V. S. Pshezhetskii, A. P. Lukyanova, and V. A. Kabanov, *J. Mol. Catalysis*, 2, 49 (1977).
30. (a) K. D. Kopple and D. E. Nitecki, *J. Am. Chem. Soc.*, 83, 4103 (1961); (b) K. D. Kopple and D. E. Nitecki, *ibid.*, 84, 4457 (1962);
(c) K. D. Kopple, R. R. Jarabak, and P. L. Bhatia, *Biochemistry*, 2, 958 (1962).
31. J. C. Sheehan and D. N. McGregor, *J. Am. Chem. Soc.*, 84, 3000 (1962).
32. A. R. Mitchell, S. K. Gupta, and R. W. Roeske, *J. Org. Chem.*, 35, 2877 (1970).
33. F. Cramer and G. Mackensen, *Angew. Chem.*, 78, 641 (1966).
34. R. L. VanEtten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *J. Am. Chem. Soc.*, 89, 3242 (1967).
35. K. Hattori *et al.*, *ibid.*, 97, 4432 (1975).
36. M. Komiyama, M. L. Bender, M. Utaka, and A. Takeda, *Proc. Natl. Acad. Sci.*, 74, 2634 (1977).
37. K. Flohr, R. M. Paton, and E. T. Kaiser, *Chem. Commun.*, 1621 (1971).
38. Y. Murakami, J. Sunamoto, and K. Kano, *Bull. Chem. Soc. Jpn.*, 47, 1238 (1974).
39. Y. Murakami, J. Sunamoto, H. Okamoto, and K. Kiyomiki, *Bull. Chem. Soc. Jpn.*, 48, 1537 (1975).
40. J. M. Brown and C. A. Bunton, *J. C. S. Chem. Commun.*, 969 (1974).
41. I. Tabushi, Y. Kuroda, and S. Kita, *Tetrahedron Lett.*, 8, 643 (1974).
42. J. Sunamoto, H. Okamoto, H. Kondo, and Y. Murakami, *ibid.*, 32, 2761 (1975).
43. M. Komiyama and M. L. Bender, *Bioorg. Chem.*, 6, 13 (1977).
44. M. Komiyama, T. R. Roesel, and M. L. Bender, *Proc. Natl. Acad. Sci. USA*, 74, 23 (1977).

THE PHOTOLYSIS OF CARBON SUBOXIDE WITH OLEFINS AND ETHERS

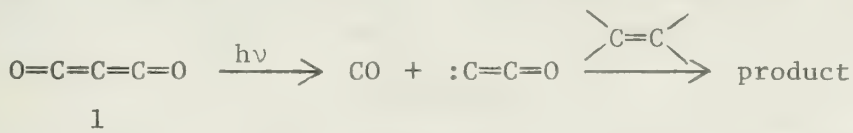
Reported by Dale K. Loth

November 27, 1978

In 1906, Diels observed that the dehydration of diethyl malonate with P_2O_5 yielded a pungent gas, which he named carbon suboxide, and assigned the structure 1.¹ Carbon suboxide is a linear molecule with an extremely low bending frequency about the central carbon.² It is very reactive, reacting with nucleophiles to give malonic acid derivatives and heterocycles, undergoing polymerizations and cycloadditions, and undergoing a photochemical reaction with a variety of organic compounds.³ The topic of this abstract is the photochemical reaction of 1 with olefins and cyclic ethers, which results in carbon atom insertion to the olefin and deoxygenation of the ether, respectively.

Early experiments by Bayes on the gas phase photolysis of 1 in the presence of ethylene revealed a simple carbon atom insertion reaction, the major products being allene and carbon monoxide, with minor amounts of propyne.⁴ Carbon atom insertion occurs for all exciting wavelengths between 2400 and 3200 Å; however, the sensitivity of the reaction toward oxygen and nitric oxide is a strong function of the wavelength. At higher wavelengths, the reaction is quenched by small amounts of oxygen and inert gasses, while at 2500 Å, oxygen has no effect on the reaction. Carbon suboxide has been photolysed in the presence of a number of small olefins, and in all cases the allene is the major product, with small amounts of the isomeric acetylene.⁵

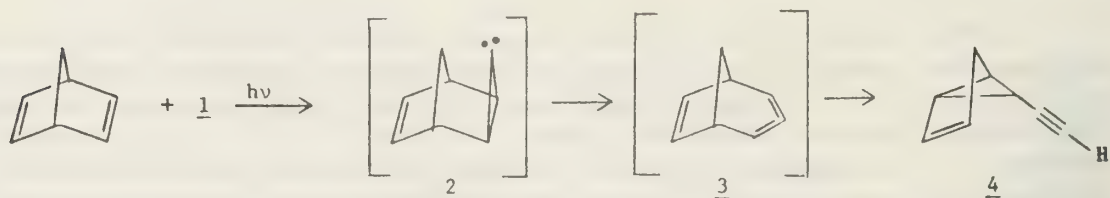
The mechanism proposed by Bayes involves photochemical decarbonylation of 1 to generate carbonyl carbene, which can exist in the triplet ground state or an excited singlet state. Carbonyl carbene has been identified in the low temperature matrix photolysis of 1. Carbonyl carbene inserts into the olefin bond generating either cyclopropylidene ketene or cyclopropylidene carbene, which is known to collapse to allenes. This is supported by isotopic labeling studies, which indicate that C-H insertion by carbonyl carbene is a minor process.⁶ The isomeric acetylenes arise from isomerization of a "hot" allene molecule or a triplet excited allene, although the dependence of the allene/acetylene ratio on total pressure indicates a more complex process.⁷ The formation of triplet allene can explain the dependence of the allene/acetylene ratio on the pressure of added inert gasses as well as the cis-trans isomerization observed in the photolysis of 1 in the presence of cis 2 butene.⁸



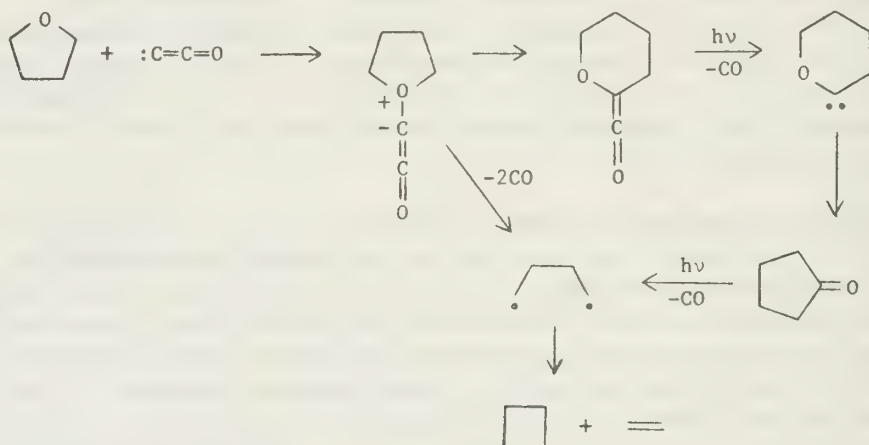
There have been several studies of the relative reactivities of olefins toward carbonyl carbene.⁹ While these results have been contradictory, it is generally believed that triplet carbonyl carbene exhibits strong electrophilic behavior, while singlet carbonyl carbene is indiscriminate in its attack on olefins.

There have been few studies of the photolysis of 1 with olefins more complex than simple ethylene derivatives. The photolysis of 1 with cyclopropenes has been well characterized, and a tetrahedrane intermediate has been invoked to explain the formation of acetylene.¹⁰ In 1971, Van Dijk and co-workers photolyzed 1 in the presence of norbornadiene. The

acetylene 4 was the only product, presumably arising from the carbene 2, which collapses to the allene 3, although other routes to 4 are possible.



In 1969, Trotmann-Dickenson observed that the photolysis of 1 with ethylene oxide and oxetane resulted in deoxygenation of the ether to give ethylene and cyclopropane, respectively.¹² This was confirmed in a later study by Shevlin *et al.*, who identified cyclobutane and ethylene as the major products from the photolysis of 1 with THF. The dependence of the cyclobutane/ethylene ratio on the extent of photolysis necessitates more than one route to the formation of either product. The following scheme is postulated:¹³



In conclusion, the photolysis of carbon suboxide in the presence of olefins is a mild and selective route to carbon atom inserted products, unlike the reaction of olefins with carbon atoms. The reactivity of 1 limits this reaction to the gas phase at moderate temperatures or perhaps to low temperature matrix techniques. Although there are no cases of the latter, it will be interesting to see if this method is employed in the future to synthesize previously unknown allenes.

BIBLIOGRAPHY

1. O. Diels and B. Wolf, *Ber. Deut. Chem. Ges.*, 39, 689 (1906).
2. W. J. Lafferty, A. G. Baki, and E. K. Flyler, *J. Chem. Phys.*, 40, 224 (1964); W. H. Weber and G. W. Ford, *J. Mol. Spectros.*, 63, 445 (1976).
3. For a brief discussion on the reaction of carbon suboxide with nucleophiles, see E. Ziegler, *Angew. Chem. Int. Ed.*, 13, 491 (1974).
4. K. D. Bayes, *J. Am. Chem. Soc.*, 83, 3712 (1961); K. D. Bayes, *ibid.*, 84, 4077 (1962).
5. K. D. Bayes, *ibid.*, 85, 1730 (1963); C. Willis and K. D. Bayes, *ibid.*, 88, 3203 (1966).
6. R. T. Mullen and A. P. Wolf, *ibid.*, 84, 3214 (1962).

7. C. Willis and K. D. Bayes, J. Phys. Chem., 71, 3367 (1967).
8. R. B. Cundall, A. S. Davies, and T. F. Palmer, ibid., 70, 2503 (1966).
9. R. T. K. Baker, J. A. Kerr, and A. F. Trotmann-Dickenson, Chem. Commun., 358 (1965); R. T. K. Baker, J. A. Kerr, and A. F. Trotmann-Dickenson, J. Chem. Soc. A, 975 (1966); D. G. Williamson and K. D. Bayes, J. Am. Chem. Soc., 90, 1957 (1968).
10. H. W. Chan, A. Lautzenheiser, and A. P. Wolf, Tetrahedron Lett., 6295 (1966); R. F. Peterson, Jr., R. K. T. Baker, and R. L. Wolfgang, ibid., 4749 (1969); P. B. Shevlin and A. P. Wolf, J. Am. Chem. Soc., 92, 406 (1970).
11. G. W. Klumpp and P. M. Van Dijk, Rec. Trav. Chim. Pays-Bas, 90, 381 (1971).
12. R. T. K. Baker, J. A. Kerr, and A. F. Trotmann-Dickenson, J. Chem. Soc. A, 390 (1969).
13. T. R. Forbus, P. A. Birdsong, and P. B. Shevlin, J. Am. Chem. Soc., 100, 6425 (1978).

CARCINOGENESIS AND TUMOR PROMOTION: A CHEMIST'S PERSPECTIVE

Reported by G. A. Krafft

November 30, 1978

It is now recognized that chemical carcinogenesis is multistep in its evolution and multifactor in its etiology.¹⁻³ Berenblum demonstrated this clearly in defining a two-stage "initiation-promotion" model for skin carcinogenesis. Several approaches have been taken in an attempt to generalize this model and elucidate the nature of the biochemical processes which are responsible for "initiation" of normal cells and "promotion" of the initiated cells to malignant tumor cells.

Early in vivo studies attempting to show an etiological link between carcinogenesis and chemical agents⁵⁻⁹ gave way to in vitro cell culture studies which sought to define the cellular metabolism responsible for carcinogenesis.^{1,3} Recent studies¹⁰ have identified certain biochemical events associated with tumor initiation and promotion, yet little evidence regarding the sequence of biochemical events which lead to chemical carcinogenesis has been obtained.

The present paper will address the specific problem of tumor promotion, within the framework of recent studies in this area, and propose experiments directed towards elucidation of the initial biochemical events of tumor promotion. An understanding of these events provides a basis for investigation of subsequent biochemical processes which lead to a malignantly transformed cell.

The Two-Stage Model of Carcinogenesis. A classic experiment in cancer research demonstrated the remarkable enhancement of tumor production by sequential treatment of mouse skin with two distinctly different chemical agents.⁹ A single small dose (10-50 μ g) of 7,12-dimethylbenz(a)anthracene (DMBA), a potent carcinogen, topically applied to mouse skin elicited no response throughout the lifetime of the animal. However, when this initiating dose of carcinogen was followed by repetitive applications of small amounts of croton oil, a noncarcinogenic irritant extracted from seeds, numerous malignant papillomas appeared within 14-18 weeks. This experiment afforded a dissection of skin carcinogenesis into two distinct but dependent processes, initiation and promotion.

The Molecular Basis of Initiation. The two-stage experiment described above established that a single encounter of mouse skin cells with a small amount of the carcinogen significantly altered them. In the absence of a subsequent promoter, however, this permanent change was not manifest. It is generally agreed that initiation occurs in the cell nucleus,³ either by altering DNA or chromatin associated protein. It has been suggested that initiation involves either somatic mutation (mutagenesis),¹¹⁻¹³ covalent binding of carcinogens to DNA,¹⁴ or the induction of error-prone DNA repair systems.¹⁵⁻¹⁷

Figure 1^{3,18-30} shows a fairly good correlation of DNA binding with initiating potency for some known carcinogens. The dashed line correlates compounds needing cellular activation and the solid line correlates the alkylating compounds. Of the two alkylating aromatic hydrocarbons, 7-bromomethylbenzanthracene, 10, and 7-bromomethyl-12-methylbenzanthracene, 9, however, the latter is the more potent initiator, but attains a significantly lower level of covalent DNA binding.³⁰ Thus, a theory of initiation involving only binding to DNA may be oversimplified.

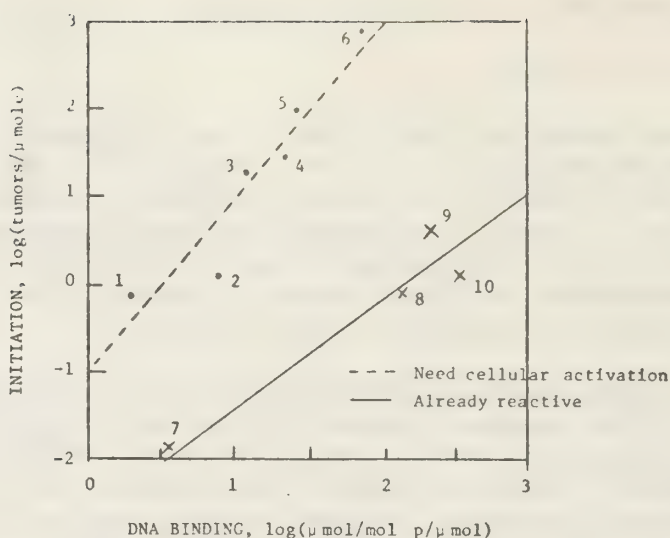


Figure 1. The relationship of tumor initiation in mouse skin to the amount of initiator bound to mouse skin DNA. (1) dibenz(a,c) anthracene;^{18,19} (2) 7-methylbenz(a)anthracene;^{20,21} (3) dibenz(a,b)anthracene;^{22,13} (4) benzo(a)pyrene;^{19,23} (5) 3-methylcholanthrene;^{19,24} (6) 7,12-dimethylbenz(a)anthracene;^{19,25} (7) 8-propiolactone;^{26,27} (8) N-methyl-N'-nitro-N-nitrosoguanidine;²⁸ (9) 7-bromomethyl-12-methylbenz(a)anthracene;^{29,30} (10) 7-bromomethylbenz(a)anthracene.³⁰

Mutagenesis has been equated with initiation,¹¹⁻¹³ but Figure 2^{18,20, 22-26,29,31-35} indicates that there is a poor correlation between initiating potency and mutagenicity for various known carcinogens. Sodium azide and ethanemethylsulfonate are examples of compounds which are mutagenic in *S. typhimurium*, but are not initiators.^{36,37} Therefore, while mutagenesis

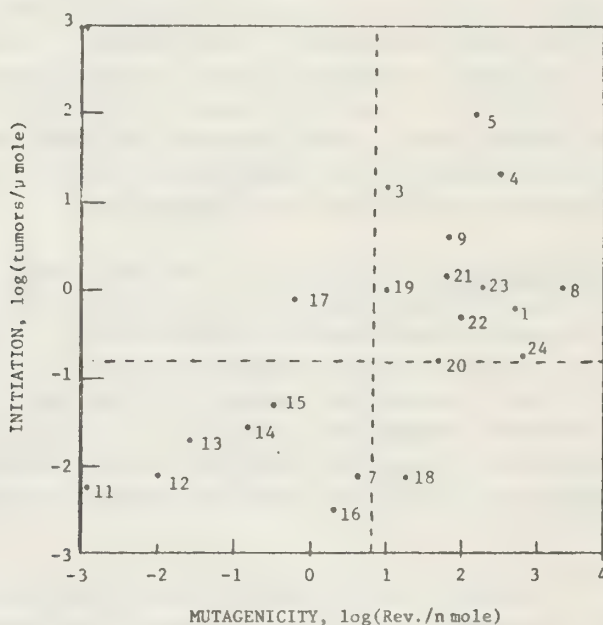
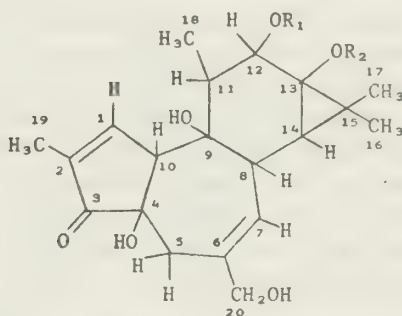


Figure 2. The relationship of initiation in mouse skin to mutagenesis in *S. typhimurium*. Mutagenicity data from McCann et al.¹³ Compound numbers 1-10 are as in Figure 1. (11) urethan;³¹ (12) anthracene;¹⁸ (13) pyrene;¹⁸ (14) diepoxybutane;³² (15) phenanthrene;¹⁹ (16) 1'-acetoxysafrole;³³ (17) benzo(c)pyrene;¹¹ (18) cyclicaldehyde;³⁴ (19) benzo(a)anthracene;¹⁸ (20) N-hydroxy-2-naphthylamine;³⁵ (21) 7-methylbenz(a)anthracene;²⁰ (22) chrysene;¹⁰ (23) N-acetoxy-2-acetamidofluorene;³⁶ (24) N-hydroxy-1-naphthylamine.³⁷

may be involved in initiation, it appears that other factors may control the efficiency of the initiation process.³⁸

A theory of initiation which extends the idea of covalent DNA binding to involvement of the ensuing repair processes appears to be more tenable.¹⁵⁻¹⁷ In this model, good initiators are molecules which create lesions on DNA incapable of being repaired by the normal constitutive repair process.³⁹ Repair of such lesions would require that a special error prone repair system be induced. It has been postulated that certain cellular functions, termed "SOS" functions, associated with the induction of this repair system are eventually responsible for malignant transformation.¹⁷ This theory has been substantiated in prokaryotic cells,³⁹ and will be addressed later, in terms of a hypothetical model for mammalian cancer.

The Molecular Basis of Tumor Promotion. A variety of compounds has been shown to have tumor promoting capabilities in a number of animal systems.³ There seems to be no unifying structural or chemical characteristics common to the diverse group of promoting agents; however, the diterpenoid phorbol diesters, 1a - 1c, are the most active promoters known⁴⁰ and will be used as models for consideration of interactions at the molecular level.



	<u>Compound</u>	<u>R₁</u>	<u>R₂</u>
<u>1a</u>	Tetradecanoyl-phorbol-acetate	Tetradecanoate	Acetate
<u>1b</u>	Phorbol-didecanoate	Decanoate	Decanoate
<u>1c</u>	Phorbol-dibenzoate	Benzoate	Benzoate

The most potent of the phorbol diesters is 12-o-tetradecanoyl-13-acetate, 1a (TPA). This compound acts as a tumor promoter at doses ≥ 2.0 mg, a level comparable to physiologically effective doses of cellular hormones. Structure-activity studies of the phorbol esters reveal a number of structural features necessary for maximum activity:^{1,40-42} (1) a primary allylic hydroxyl at C-20, (2) an α,β -unsaturated keto group at C-3, (3) a long chain fatty acid ester at C-12, (4) a short chain fatty acid ester at C-13, (5) β -orientation of the 4-hydroxyl group and (6) an intact β cyclopropane ring.

The rigid structural requirements for maximal promoting activity of the phorbol diesters and the extremely low levels at which TPA elicits a promoting response lead to the hypothesis that a specific hormone-like interaction occurs and is mediated by the initial formation of a TPA-receptor complex. It is reasonable to suggest that a receptor exists in the cell to mediate specific regulatory processes associated with growth and replication, via interaction with one or more endogenous controlling substances, and that TPA, acting as a psuedo-agonist, interacts with such

a receptor to alter or interrupt the biochemical responses normally mediated by the receptor, thereby bringing about tumor promotion.

Evidence exists which implicates the cell membrane as the site of such a receptor.⁶⁷ Within several minutes of the TPA treatments, cells exhibited a marked dose-dependent change in membrane permeability, as measured by $^{32}\text{P}_i$ and $^{86}\text{Rb}^+$ uptake,^{48,59} and increased ^3H -deoxyglucose transport.^{49,59} Autoradiographic studies of [^3H -20]-TPA treated cells demonstrated selective localization of TPA at the cell surface.⁶⁷ TPA also has been shown to inhibit binding of epidermal growth factor to its membrane receptor. Additionally, alterations by TPA of lipid metabolism^{46,56} and prostaglandin binding and synthesis,^{43,67} both thought to be mediated by membrane receptors, and fluorescence studies of TPA treated membranes⁶⁸ suggest a membrane receptor as the initial site of TPA action.

TPA induces DNA, RNA and protein synthesis in normal and initiated cells,^{47,50-54} induces mitogenesis,^{50,51} and brings about phosphorylation and fragmentation of chromatin associated proteins called histones,^{53,55,59} all of which are involved in gene activation. Several studies have reported significant cellular dedifferentiation as a result of this TPA induced gene activation.⁷⁰⁻⁷⁵ These responses are reversible in normal cells upon removal of TPA from the cell structures.

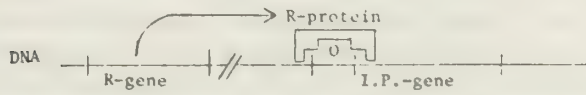
Enzyme activity within TPA treated cells is altered through gene activation, transcription, and *de novo* protein synthesis.^{43,62,63} Induction of ornithine decarboxylase (ODC), a polyamine biosynthetic enzyme, correlates well with the promoting activity of several phorbol diesters, and is a dose dependent response with TPA.^{61-63,76} It is doubtful that ODC activity is obligatory for tumor promotion, inasmuch as promotion occurs in mice deficient in the ODC cofactor, vitamin-B₆.⁷⁷ Promotion by TPA in cells treated with α -difluoromethylornithine,^{78,79} an ODC suicide inhibitor, would verify this.

Plasminogen activator (PA), a protease enzyme, is also induced by TPA in a dose dependent manner.^{64,65} This is significant in that gene activation is thought to occur by proteolytic action of inducer proteases on gene-repressor proteins.⁸⁰ PA activity has been observed in virally transformed cells,⁸¹⁻⁸³ and may act in precisely this manner, to bring about malignant transformation. This might occur by protease induction of SOS functions,¹⁷ as shown in the hypothetical scheme of Figure 3.

Normal cells (Figure 3a) have numerous unexpressed genes including the I.P.-gene which codes for one or several inducer proteases. The R-gene codes for R-protein which represses the I.P.-gene. TPA, acting on normal cells (Figure 3b), in some way blocks or inactivates R-protein, inducing I.P.-gene and synthesis of inducer protease (I.P.). I.P. activates SOS genes by proteolysis of SOS repressor proteins, which express SOS functions, *e.g.* error-prone repair, mitosis and growth. These effects are reversible. Initiated cells (Figure 3c) have one or more unrepaired DNA lesions, and a few cells have a lesion on the R-gene. TPA treatment of initiated cells (Figure 3d) induces SOS functions, including SOS-error-prone repair, which eventually repairs the lesion, but introduces a mutational error into the R-gene (Figure 3e). The mutant R-gene produces no R-protein, so that the I.P. gene is permanently expressed. Permanent SOS expression, *e.g.* growth and mitosis, constitutes malignancy.

Figure 3. A hypothetical model for two-stage carcinogenesis.

(a) Normal Cell

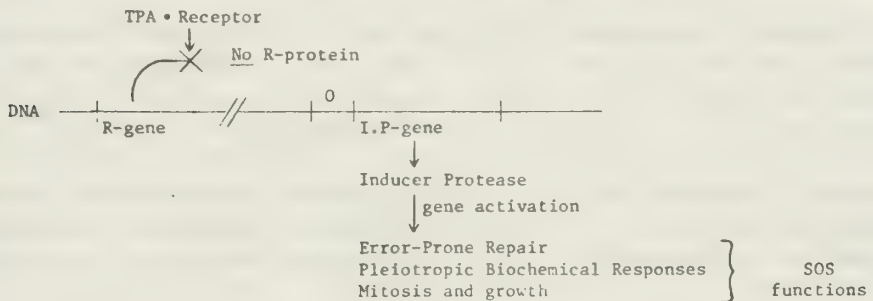


R-gene: Codes for a Repressor protein

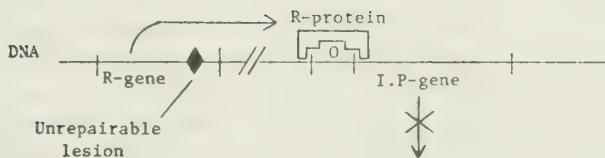
I.P.-gene: Codes for an Inducer Protease enzyme

O: Start signal for I.P. Gene

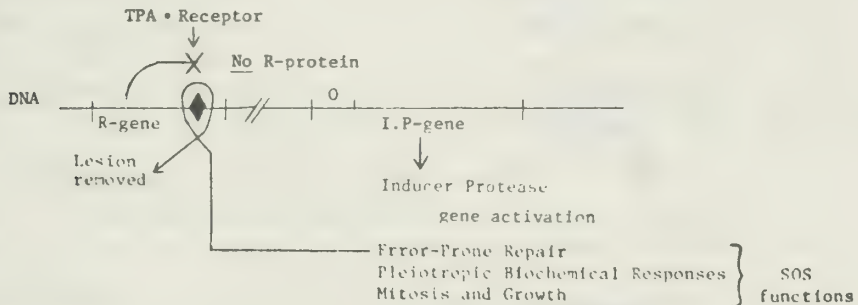
(b) Normal Cell + TPA



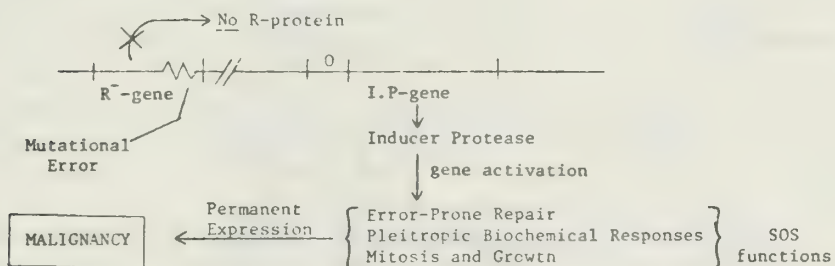
(c) Initiated Cell



(d) Initiated Cell + TPA



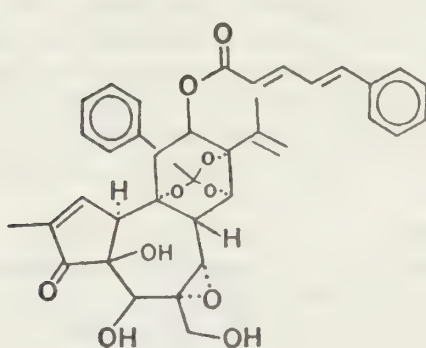
(e) Repaired R⁻ Mutant Cell



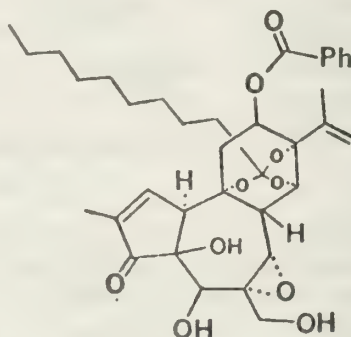
A number of TPA induced responses can be antagonized, and tumor promotion blocked by various substances. Several protease inhibitors, tosyllysine chloromethyl ketone (TLCK), tosylarginine methyl ester (TAME), antipain and leupeptin, block TPA induced promotion,^{43,84,85} presumably by inactivation of PA or other inducer proteases. These and other protease inhibitors also block induction of prokaryotic SOS functions.^{17,43} Anti-inflammatory glucocorticoids including dexamethasone, fluocinolone acetonide and fluocinonide inhibit TPA induced PA and ODC activity in a dose dependent manner, and also block DNA synthesis and tumor promotion.^{2,87} In a similar way, 10,11-epoxyretinoic acid, 5,6-epoxy- β -ionone and insect juvenile hormone antagonize TPA induced responses.⁹²⁻⁹⁵ These three compounds, and perhaps the glucocorticoids, may antagonize by direct interaction with the TPA receptor.

Several daphnane diterpenes which are structurally related to the phorbol esters (Figure 4)⁹⁶⁻⁹⁹ may act as antagonists and agonists. These compounds exhibit significant anti-tumor activity in mouse leukemias^{96,97,102} but, like the active phorbol esters, induce PA activity. It is particularly interesting that substitution of the 6,7 epoxide with a double bond obliterates the anti-tumor activity and gives weak promoting activity.¹⁰¹ These compounds need to be more thoroughly studied to define requirements for promoting and anti-tumor activity.

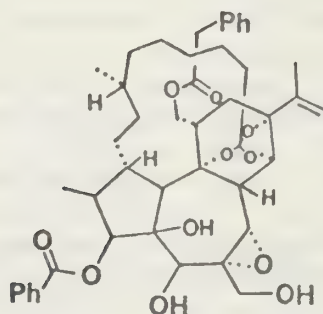
Figure 4. Anti-leukemic daphnane diterpenes



Mezerein



Gnidilatin



Gnidimacrin

A Chemically Rational Approach to the Problem of Tumor Promotion.

A large body of evidence has been summarized above to implicate a specific receptor molecule as the mediator for tumor promotion and other biochemical responses associated therewith. A number of questions can be raised with respect to the specific molecular interactions responsible for tumor promotion. Can a specific receptor site be defined? How do promotion agonists interact at this site? What aspects of antagonist interactions distinguish them from agonist interactions, or how do we distinguish the agonist/antagonist activities of various substances on a molecular basis? Finally, how do the molecular interactions at the receptor binding site translate into a given spectrum of receptor-complex activities? Several experimental approaches designed from a chemical perspective will be needed to answer these questions. If successful, such studies would permit a detailed understanding of tumor promotion and carcinogenesis.

BIBLIOGRAPHY

1. R. K. Boutwell, CRC Crit. Rev. of Toxic., 2, 419 (1974).
2. I. B. Weinstein, M. Wigler, and C. Pietropaolo, in "The Origins of Human Cancer", Cold Spring Harbor, N.Y., 1977, p. 751.
3. J. D. Scribner, and R. Süss, Int. Rev. of Exptl. Path., 18, 137 (1978).
4. I. Berenblum and P. Shubik, Br. J. Cancer, 1, 383 (1947).
5. I. Berenblum, Cancer Res., 1, 44 (1941).
6. I. Berenblum, Cancer Res., 1, 807 (1941).
7. J. C. Mottram, J. Pathol. Bacteriol., 56, 181 (1944).
8. I. Berenblum and N. Haran, Br. J. Cancer, 9, 268 (1955).
9. R. K. Boutwell, Prog. Exp. Tumor Res., 4, 207 (1964).
10. T. J. Slaga, A. Sivak, and R. K. Boutwell (eds.), "Carcinogenesis: A Comprehensive Survey", Vol. 2, Raven Press, New York, N.Y., 1978.
11. B. N. Ames, W. E. Durston, and F. D. Lee, Proc. Nat. Acad. Sci. U.S.A., 70, 2281 (1973).
12. J. McCann and B. N. Ames, Proc. Nat. Acad. Sci. U.S.A., 73, 950 (1976).
13. J. McCann, E. Choi, E. Yannasakis, and B. N. Ames, Proc. Nat. Acad. Sci. U.S.A., 72, 5135 (1975).
14. P. Brookes, Life Sci., 16, 331 (1975).
15. M. Radman, in "Molecular Mechanisms for Repair of DNA", P. C. Hanawalt and R. B. Setlow, eds., Part A, Plenum, New York, N.Y., 1975, p. 355.
16. M. Radman, in "Proceedings of the Colloque International de Canciologine Chimique", July, 1976, Paris, France.
17. M. Radman, G. Villani, S. Boiteux, M. Defais, P. Caillet-Gauget, and S. Spadari, in "Origins of Human Cancer", J. D. Watson and H. Hiatt, eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1977, p. 903.
18. J. D. Scribner, J. Natl. Cancer Inst., 50, 1717 (1973).
19. P. Brookes and P. D. Lawley, Nature, 202, 781 (1964).
20. E. C. Miller and J. A. Miller, Proc. Soc. Exp. Biol. Med., 124, 915 (1967).
21. W. M. Baird, and P. Brookes, Cancer Res., 33, 2378 (1973).
22. G. T. Bowden, T. J. Slaga, B. G. Shapas, and R. K. Boutwell, Cancer Res., 34, 2634 (1974).
23. T. J. Slaga, A. Viaje, D. L. Berry, W. Braken, S. G. Buty, and J. D. Scribner, Cancer Lett., 2, 115 (1976).
24. J. D. Scribner and T. J. Slaga, Cancer Res., 33, 542 (1973).

25. T. J. Slaga, J. D. Scribner, J. M. Rice, S. B. Das, and S. Thompson, *J. Natl. Cancer Inst.*, 53, 1337 (1974).
26. N. H. Colburn and R. K. Boutwell, *Cancer Res.*, 26, 1701 (1966).
27. N. H. Colburn and R. K. Boutwell, *Cancer Res.*, 28, 653 (1968).
28. G. T. Bowden and R. K. Boutwell, *Cancer Res.*, 34, 1552 (1974).
29. A. Dipple and T. A. Slade, *Eur. J. Cancer*, 7, 473 (1971).
30. M. P. Rayman and A. Dipple, *Biochemistry*, 12, 1538 (1973).
31. H. Hennings, G. T. Bowden, and R. K. Boutwell, *Cancer Res.*, 29, 1773 (1969).
32. B. L. Van Duuren, *Ann. N. Y. Acad. Sci.*, 163, 633 (1969).
33. P. Borchert, J. A. Miller, E. C. Miller, and T. K. Shires, *Cancer Res.*, 33, 590 (1973).
34. F. Mukai and W. Troll, *Ann. N. Y. Acad. Sci.*, 163, 828 (1969).
35. J. D. Scribner and T. J. Slaga, *J. Natl. Cancer Inst.*, 54, 491 (1975).
36. R. Devoret and M. Blanco, *Mol. Gen. Genet.*, 107, 272 (1970).
37. P. Moreau and R. Devoret, in "Origins of Human Cancer", J. D. Watson and A. Hiatt, eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1977, p. 1451.
38. A. Sivak, *Science*, 193, 272 (1976).
39. E. M. Witkin, *Bacteriol. Rev.*, 40, 869 (1976).
40. E. Hecker, reference 10, p. 11.
41. H. W. Thielmann and E. Hecker, in "Fortshritte der Krebsforschung", G. C. Schmidt and D. Vetter, eds., Schattauer Verlag, New York, 1969, p. 171.
42. G. Kreibach and E. Hecker, *Z. Krebsforsch.*, 74, 448 (1970) and references therein.
43. S. Belman and W. Troll, reference 10, p. 117.
44. L. S. Lee and I. B. Weinstein, *Science*, 202, 313 (1978).
45. A. Sivak, B. T. Mossman, and B. L. Van Duuren, *Biochem. Biophys. Res. Commun.*, 46, 605 (1971).
46. B. L. Van Duuren, in "Chemical Carcinogens", C. E. Searle, ed., ACS Monograph 173, 1976, p. 24.
47. P. M. Blumberg, P. E. Dreidger, and P. W. Rossow, *Nature*, 264, 446 (1976).
48. J. Moroney, A. Smith, L. D. Tomei, and C. E. Wenner, *J. Cell Physiol.*, 95, 287 (1978).
49. P. E. Dreidger and P. M. Blumberg, *Cancer Res.*, 37, 3257 (1977).
50. S. H. Yupsa, T. Ben, E. Patterson, T. Michael, K. Elgjo, and H. Hennings, *Cancer Res.*, 36, 4062 (1976).
51. A. R. Peterson, S. Mondel, D. W. Brankow, W. Thon, and C. Heidelberger, *Cancer Res.*, 37, 3223 (1977).
52. A. Sivak and B. L. Van Duuren, *Cancer Res.*, 30, 1203 (1970).
53. A. Balmain, A. Alonso, and J. Fischer, *Cancer Res.*, 37, 1548 (1977).
54. W. M. Baird, J. A. Sedgwick, and R. K. Boutwell, *Cancer Res.*, 31, 1434 (1971).
55. R. Raineri, R. C. Simsiman, and R. K. Boutwell, *Cancer Res.*, 37, 4584 (1977).
56. P. W. Wertz, and G. C. Mueller, *Cancer Res.*, 38, 2900 (1978).
57. M. A. G. Virji, M. W. Steffes, and R. D. Estensen, *Endocrinology*, 102, 706 (1978).
58. A. Balmain, reference 10, p. 153.
59. A. Balmain and E. Hecker, *Biochim. Biophys. Acta*, 362, 457 (1974).
60. A. Balmain and E. Hecker, *Z. Krebsforsch.*, 86, 251 (1976).
61. S. Matsuzaki, T. Kakegawa, M. Suzuki, and K. Hamana, *Endocrinol. Japan*, 25, 129 (1978).
62. R. K. Boutwell, reference 10, p. 49.

63. R. K. Boutwell, in "The Origins of Human Cancer", J. D. Watson and H. Hiatt, eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1977, p. 773 and references therein.
64. I. B. Weinstein, in reference 10, p. 313.
65. M. Wigler and I. B. Weinstein, *Nature*, 259, 232 (1976).
66. R. A. Mufson, reference 10, p. 135.
67. C. E. Wenner, J. Moroney, and C. W. Porter, reference 10, p. 363.
68. B. L. Van Duuren, S. Banerjee, and G. Witz, *Chem.-Biol. Interactions*, 15, 233 (1976).
69. G. C. Mueller, T. W. Kensler, and T. Kajiwara, reference 10, p. 79.
70. L. Diamond, T. G. O'Brien, and G. Rovera, reference 10, p. 335.
71. L. Diamond, T. G. O'Brien, and G. Rovera, *Nature*, 269, 247 (1977).
72. R. Cohen, M. Pacifici, N. Rubinstein, J. Biehl, and H. Holtzer, *Nature*, 266, 538 (1977).
73. G. Rovera, T. G. O'Brien, and L. Diamond, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 2894 (1977).
74. H. Yamasaki, E. Fibach, U. Nudel, I. B. Weinstein, R. A. Rifkind, and P. A. Marks, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 3451 (1977).
75. A. N. Raick, *Cancer Res.*, 34, 2915 (1974).
76. T. G. O'Brien, *Cancer Res.*, 36, 2644 (1976).
77. A. W. Murray, *Experientia*, 34, 691 (1978).
78. N. J. Prakash, P. J. Schechter, J. Grove, and J. Koch-Weser, *Cancer Res.*, 38, 3059 (1978).
79. B. Metcalf, P. Bey, C. Danzin, M. J. Jung, P. Casara, and J. P. Vever, *J. Am. Chem. Soc.*, 100, 2551 (1978).
80. W. Troll, T. Rossman, J. Katz, M. Levitz, and T. Sugimura, in "Proteases and Biological Control", E. Reich, D. B. Rifkin, and E. Shaw, eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1975, p. 977.
81. M. J. Weber, A. H. Hale, and D. E. Roll, *ibid.*, p. 915.
82. A. R. Goldberg, B. A. Wolf, and P. A. Lefebvre, *ibid.*, p. 857.
83. J. K. Christman, G. Acs, S. Silagi, and S. C. Silverstein, *ibid.*, p. 827.
84. W. Troll, A. Klassen, and A. Janoff, *Science*, 169, 1211 (1970).
85. S. Belman, T. Rossman, and W. Troll, *AACR, Abstr.* #126 (1977).
86. M. S. Meyn, T. Rossman, and W. Troll, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 1152 (1977).
87. T. J. Slaga, S. M. Fischer, A. Viaje, D. L. Berry, S. LeClerc, and D. R. Miller, reference 10, p. 173.
88. S. H. Yupsa, U. Lichti, H. Hennings, T. Ben, E. Patterson, and T. J. Slaga, reference 10, p. 245.
89. S. Belman and W. Troll, *Cancer Res.*, 32, 450 (1972).
90. T. J. Slaga, U. Lichti, H. Hennings, K. Elgjo, and S. H. Yupsa, *J. Natl. Cancer Inst.*, 60, 425 (1978).
91. A. Viaje, T. J. Slaga, M. Wigler, and I. B. Weinstein, *Cancer Res.*, 37, 1530 (1977).
92. T. W. Kensler and G. C. Mueller, *Life Sciences*, 22, 505 (1978).
93. P. W. Wertz, T. W. Kensler, and G. C. Mueller, *Biochem. Biophys. Res. Commun.*, 83, 138 (1978).
94. T. W. Kensler, A. K. Verma, R. K. Boutwell, and G. C. Mueller, *Cancer Res.*, 38, 2896 (1978).
95. A. K. Verma and R. K. Boutwell, *Cancer Res.*, 37, 2196 (1977).
96. F. J. Evans and C. J. Soper, *Lloydia*, 41, 193 (1978).
97. S. M. Kupchan, Y. Shizuri, W. C. Sumner, Jr., H. R. Haynes, A. P. Leighton, and B. R. Sickles, *J. Org. Chem.*, 41, 3850 (1976).
98. S. M. Kupchan and R. L. Baxter, *Science*, 187, 652 (1974).

99. S. M. Kupchan, I. Uchida, A. R. Branfman, R. G. Dailey, Jr., and B. Yu Fei, *Science*, 191, 571 (1976).
100. M. Wigler, D. DeFeo, and I. B. Weinstein, *Cancer Res.*, 38, 1434 (1978).
101. R. J. Schmidt and F. J. Evans, *J. Pharm. Pharmacol.*, 27, 50 (1975).
102. M. Ogura, K. Koike, G. A. Cordell, and N. R. Farnsworth, *Planta Medica*, 33, 128 (1978).

SPIN TRAPPING OF SHORT LIVED FREE RADICALS

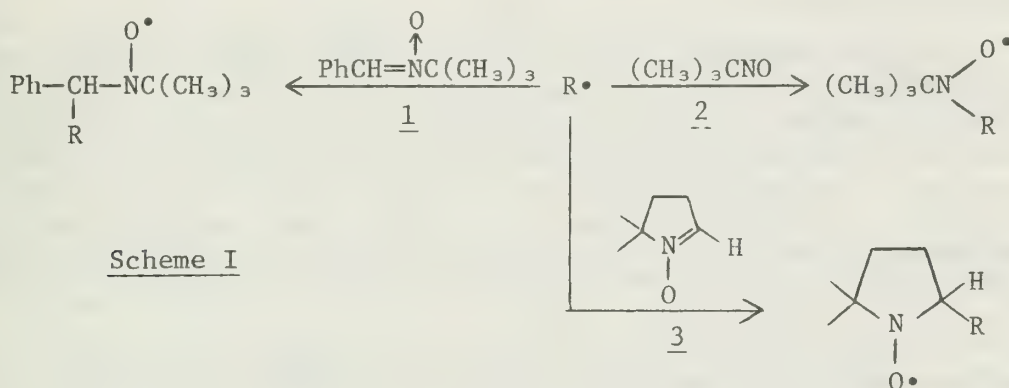
Reported by Thomas Sullivan

December 4, 1978

The problem of the detection and characterization of short lived intermediates is of considerable interest in the investigation of reaction mechanisms. Several methods, including rapid mixing flow systems, low temperatures and in situ high flux irradiation techniques have been applied with varying degrees of success to a number of systems. Recently, the detection of short lived free radical intermediates has been facilitated by the addition of such radicals to nitrones or nitroso compounds to produce the more stable nitroxide radical. This technique is termed spin trapping, the nitron and nitroso compounds are called spin traps and the addition products are known as spin adducts.¹ The structure of this nitroxide radical is indicated by the hyperfine coupling constants (hfcc's) and g values in the esr spectrum thereby providing identification of the original radical.

Spin trapping derives its name from the related techniques of radical trapping and spin labelling. Spin labelling² involves observation of the esr signal of a nitroxide radical in a biological system. The esr spectrum is highly dependent on the environment in the vicinity of the radical center; thus, deductions can be drawn about the chemical environment around the radical.

A variety of nitron and nitroso spin traps, with differing advantages and disadvantages, have been described in the literature.^{1,3-5,9-11,15,25} The generally used and commercially available traps include phenyl-t-butylnitron or PBN (1), nitroso-t-butane (2-methyl-2-nitrosopropane) or NtB (2), and 5,5-dimethyl-1-pyrroline-1-oxide or DMPO (3). The spin trapping reaction is illustrated with these compounds in Scheme I:



Scheme I

Nitroso Spin Traps. The main advantage of using nitroso compounds as spin traps is that information concerning the structure of the trapped radical is easily extracted from the spectrum.¹ The multiplicity of the splitting pattern immediately gives the number of hydrogens attached to the carbon of the alkyl radical trapped. Tertiary nitroso compounds are preferred since no extraneous splitting from the spin trap itself is observed, tautomerization to the oxime is prevented, and the adduct is generally more stable. Although nitrosobenzene has been used as a spin trap, its spin adducts show hyperfine structure due to splitting by ring hydrogens. Several ring substituted nitrosobenzenes have been used as traps in order to lessen this effect.³ The line broadening due to the γ -hydrogens of NtB is sometimes a hinderance to the evaluation of

a spectrum. To overcome this problem, perdeuterionitroso-t-butane⁴ has been used successfully and found to give much narrower line widths, allowing resolution of long range coupling in undecyl radicals and hfc due to the methyl group in trapped carboxymethyl radicals which could not be seen with NtB.

When aryl radicals are trapped with nitroso compounds the additional hyperfine splitting from the ring can be used to help identify the radical. If a radical with the electron having spin density on an atom with a nuclear spin is trapped, the spin adduct has additional characteristic hfc which aids in structural assignment.

The magnitude of the nitrogen hfcc, A_N , and the G value of the nitroxide radical vary substantially according to the groups attached. For instance, $A_N = 13-16G$ for dialkyl nitroxides, 27-28G for alkoxy alkyl nitroxides, 17-18G for thiyl alkyl nitroxides, and 7-8.5G for acyl alkyl nitroxides. Aryl groups attached to the nitroxide decrease A_N due to delocalization of the electron, thereby lowering the spin density on nitrogen. The G value tends to increase with increasing atomic number due to spin-orbit coupling. The electronegativity of the radical also helps determine the G value by controlling, along with solvent, the



degree of contribution of structure 4a to the nitroxide radical center and so affects the spin density on nitrogen. For instance, the NtB adduct of the hydroxymethyl radical has a G value of 2.0060, whereas in the *n*-butylthio adduct of NtB the G value is 2.0070.⁵

Nitroso compounds also have some disadvantages as spin traps. The strong tendency of nitroso compounds to dimerize means that the concentration of material available for trapping may be less than stoichiometric. Significant amounts of nitrosobenzene and NtB exist in the dimer form in solution. Nitrosoadamantane, on the other hand, has been found to be monomeric in solution and has been used to trap the trifluoro- and trichloromethyl radicals.⁶ Since only the monomeric species is capable of spin trapping this is of considerable value.

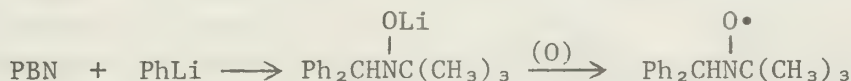
Certain spin adducts of nitroso compounds are unstable. Since the radical center is bound directly to the nitrogen, a reverse reaction can occur. For example, generation of the trityl radical in the presence of NtB produces no spin adducts, and if the nitroxide is generated independently it is not stable.⁷

Nitroso compounds are not particularly stable. Red light or moderate heat produces di-t-butylnitroxide and nitric oxide from NtB. The spectrum of this can seriously overlap with that of the desired spin adduct.

Nitrone Spin Traps. Nitrones have an advantage as spin traps in that they are generally stable compounds. They are monomeric in solution, being totally available for spin trapping. Their adducts are also fairly stable but are less informative as to the structure of the original radical. The radical adds at a site remote from the nitroxide center.

This remoteness makes identification of the structures more difficult to interpret since the spectrum invariably consists of only a triplet of doublets due to the nitrogen and βH , respectively. The magnitude of A_N and A_H^β depend on the bulk and electronegativity of the trapped radical, but these are not necessarily unique in each case. These parameters, however, are useful for identification of the spin adduct.

Nitrones are susceptible to attack from organometallic reagents and, if subsequently oxidized by trace oxygen, will produce the corresponding



nitroxide radical.⁸ This is a disadvantage when the possibility of both anionic and radical pathways exist. Rigorous deoxygenation of reaction mixtures must be done before a spin-trapping experiment is performed. This reaction can be used to advantage, however, in the production of known nitroxide radicals for comparison of their spectra to that of an unknown radical under the same conditions.

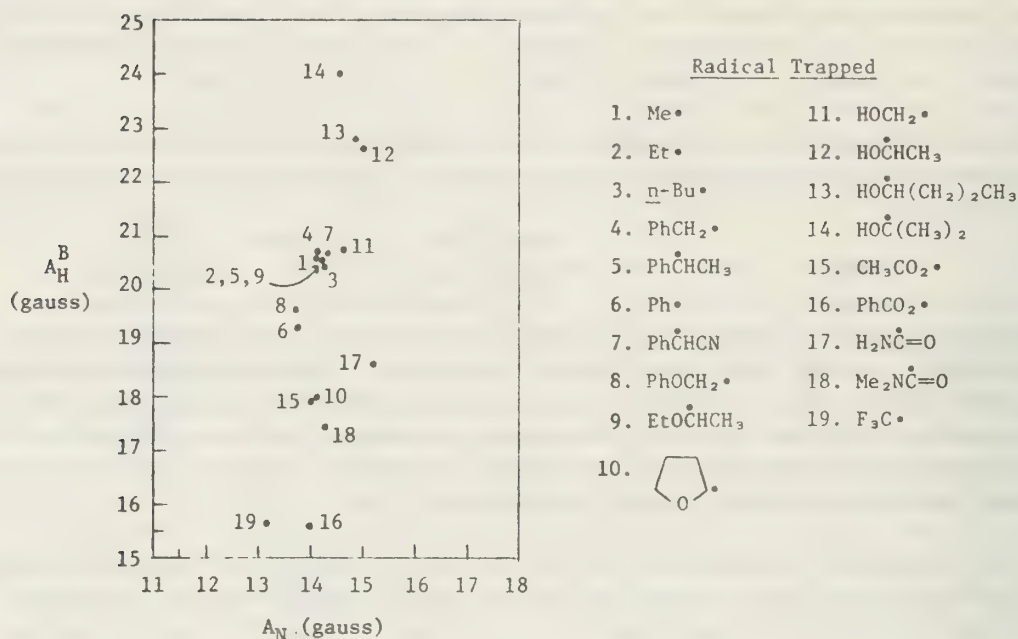
In the case of both nitrone and nitroso spin traps, the nitroxide radicals produced are generally sufficiently stable to the reaction conditions to provide good spectra. In some cases the spin trap is actually a stable, isolable compound.

Further factors affecting the spectral parameters of the spin adducts are the distance of a given atom from a radical center, the hybridization of the orbital in which the unpaired electron is located, the dihedral angle of a particular bond with respect to that orbital, and the spin density at the atom under consideration.⁹

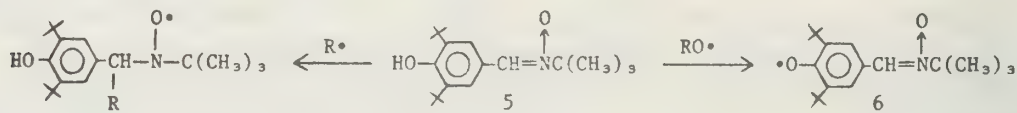
Structural Deductions from Spin Adducts. An excellent review article by E. G. Janzen¹ on spin trapping covers the literature up to 1971. This includes preliminary work on PBN, NtB, and DMPO. Cases of trapping and characterizing alkyl, alkoxy, acyl and aryl radicals are reported as well as preliminary evidence of halogen and hydrogen atom trapping. This abstract will cover work completed since Janzen's article.

Janzen has shown that with 0.05 M solutions of the cyclic nitrone 3 in benzene several different radicals can be trapped and distinguished.¹⁰ Figure 1 shows a graph of the hfcc's for the nitrogen vs. βH atoms. These data can be used to identify the radicals observed although the reliability of the assignment is dependent on the types of radicals involved. It is clear from the figure that structures corresponding to points 1-5, 7, 9, 11 or 12, 13 or 10, 15 cannot be unambiguously assigned from their spectra alone. All other points, however, differ significantly from each other and can be identified.

Figure 1. Plot of A_N vs. A_H^B for DMPO spin adducts; ± 0.15 G.

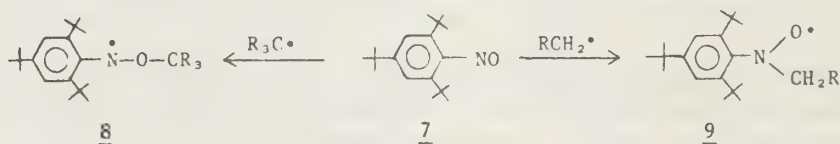


Another method of distinguishing radicals based on their reactivity with a spin trap invokes the bifunctional trap 3,5-di-*t*-butyl-4-hydroxyphenyl-*t*-butylnitron (5).¹¹ This trap gives normal spin adducts with carbon-centered radicals. Oxy radicals, however, abstract the phenolic hydrogen to produce the stable phenoxy radical 6. Since the esr spectra



of the two products are quite different, the carbon- and oxygen-centered radicals are readily distinguished. A similar result is obtained when a mixture of 2,4,6-tri-*t*-butylphenol and PBN¹² is used to trap radicals. This system has the advantage of allowing control of the ratio of the two sites of attack. In some cases visual determination of the type of radical present is possible since, in high concentrations, the phenoxy radical is blue whereas the nitroxide adduct is brown.

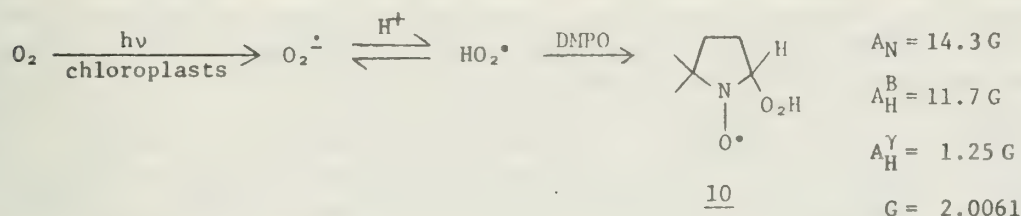
Another spin trap that yields useful structural information is 2,4,6-tri-*t*-butylnitrosobenzene (7).¹³ Like nitrosoadamantane, this spin trap is completely monomeric in solution and therefore totally available for trapping. This trap reacts differently with tertiary and



primary radicals. Due to steric crowding around the nitroso function, tertiary radicals add to oxygen to give the anilino radical 8 as the

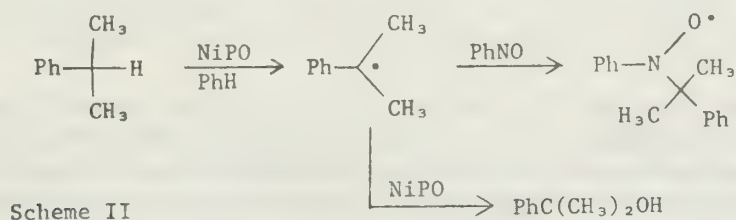
only observable product while primary radicals give exclusively the nitroxide radical 9 from normal addition to nitrogen. Secondary radicals yield a mixture of the two spin adducts, the ratio of which depends on the nature of the radical.

Application to Biological Systems. In the first application of spin traps to biological systems¹⁴ spinach chloroplasts were irradiated in an aqueous system saturated with oxygen. The hydroperoxy radical adduct was observed, presumably formed from the superoxide radical with which it is in equilibrium. The structural assignment was made by comparison of the spectral parameters to those in the literature¹⁵ for structure 10 produced by an independent method. This experiment is taken to confirm the presence of the often postulated superoxide radical in biochemical systems. The actual species trapped appears to be the hydroperoxy radical rather than superoxide followed by protonation since anion radicals have not been known to add to DMPO.

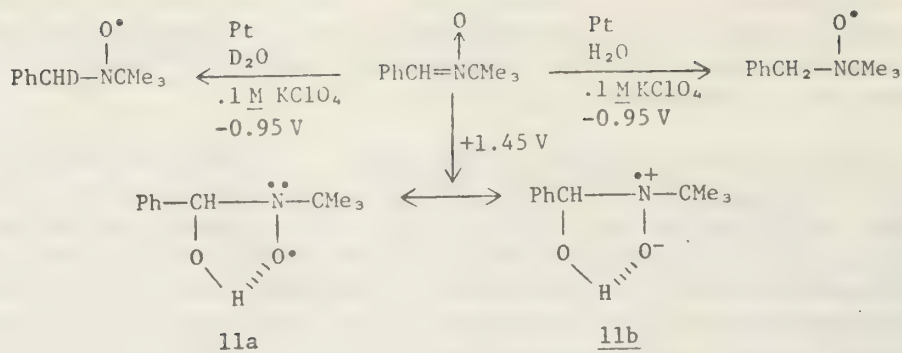


Mechanistic Investigations. Spin traps have been used to elucidate the mechanisms of a wide variety of free radical reactions. These studies include allylic brominations using N-bromosuccinimide,¹⁶ chlorinations using *t*-butyl hypochlorite,¹⁷ electrochemical¹⁸ and chemical¹⁹ reductions of phenyldiazonium salts, and trapping radicals in the gas phase,²⁰ among others.

The oxidizing agent nickel peroxide (NiPO), for example, has been postulated to function by a free radical mechanism.²¹ The oxidation of cumene to α,α -dimethylbenzyl alcohol with NiPO in deoxygenated benzene has been studied by spin trap techniques.²² Scheme II shows how nitrosobenzene intercepts the dimethylbenzyl radical during the oxidation. Since nitrosobenzene is not susceptible to attack by anions in this fashion the cumyl anion is not the active species and the cumyl radical is established as the intermediate.

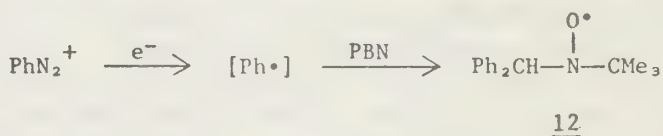


The mechanism of the electrolysis of water to produce hydrogen and oxygen presumably involves the hydrogen atom and the hydroxyl radical as intermediates. In a recent study, in situ trapping of these radicals has been accomplished using PBN.²³ When the cathodic product is observed by esr a 1:1:1 triplet of 1:2:1 triplets is observed due to the nitrogen ($I=1$) and two methylene hydrogens, respectively. When D_2O is electroly-



sized a 1:1:1 triplet of 1:1 doublets of 1:1:1 triplets is observed due to the nitrogen, one methylene hydrogen and one methylene deuterium ($I=1$), respectively. When the anodic product was observed, the hydroxyl radical adduct 11 was identified by its 1:1:1 triplet of 1:1 doublets. D_2O produced an identical spectrum. Apparently, there is hydrogen bonding in the spin adduct of the hydroxyl radical, as evidence by the high A_N and A_H^β parameters observed. Values of $A_N=20.2 \text{ G}$ and $A_H^\beta=28.9 \text{ G}$, as opposed to normal values of about 13-16 and $<5.4 \text{ G}$, respectively, are obtained. This intramolecular H-bonding from the hydroxyl hydrogen to the nitroxide oxygen is suggested to allow a larger contribution from canonical form 11b which puts more spin density on the nitrogen, thereby increasing A_N . The H-bonded structure also has a puckered ring which decreases the dihedral angle between the C-H bond and the p-orbital on nitrogen, thereby increasing A_H^β . This effect was also found in the case of hydroxyalkyl radicals trapped with DMPO (*vide supra*). The hydroxyl hydrogen does not contribute to the splitting pattern despite its proximity to the radical center because it is located on the nodal plane of the N-O π^* bond. A control reaction indicated that PBN was neither oxidized nor reduced at the range of voltage used and that no signal was observed without an applied current.²⁹

In another electrochemical reduction the phenyl radical was trapped and characterized.¹⁸ Phenyl diazonium fluoborate (0.01 M) in acetonitrile was reduced at a mercury pool cathode at 0° and -0.2 V in the presence of 0.01 M PBN. After 5 minutes, the spin adduct 12 was observed via esr.

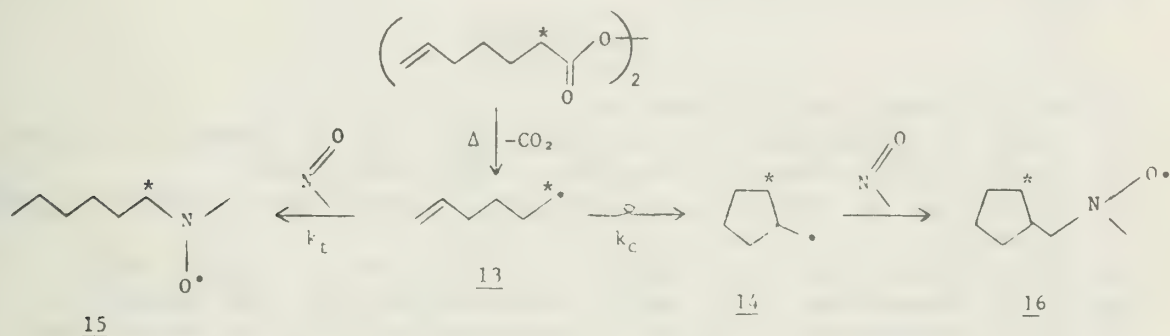


Control reactions with no current and no diazonium salt gave no observable signal. In an attempt to rule out a two-electron reduction to the phenyl anion followed by addition to PBN, a saturated solution of carbon dioxide in acetonitrile was used as solvent. Upon reaction followed by acidification, however, no benzoic acid was formed. This indicates that phenyl anion was not involved and provides proof of the existence of the phenyl radical, a species that has not been observed directly under normal reaction conditions.

Kinetic Studies. The kinetics of spin trapping, termed spin counting,²⁴ is just beginning to be studied. A number of factors are necessary for this technique to be successful. The spin adduct signal must be seen to increase as a function of time, both the trap and adduct must not affect the rate of free radical production, and the rate of trapping must be much greater than the rate of production of free radicals.

In the first of a series of articles, Schmid and Ingold have described the competition of a reaction with a known rate to that of spin trapping.²⁵ The cyclization of the 5-hexenyl radical (13) to the cyclopentylmethyl radical (14) proceeds at a rate of about $1.8 \times 10^5 \text{ sec}^{-1}$ at 40° . This value is obtained by extrapolation of an Arrhenius plot developed by an esr study of the cyclization²⁶ and independently from the kinetics of the reaction of n-hexyl bromide with tri-butyltin hydride along with product composition data for 5-hexenyl bromide with the same reagent.²⁷ In competition with this cyclization is the spin trapping of 13 to give the spin adduct.

The 5-hexenyl radical is produced by thermolysis of heptanoyl peroxide and allowed to react with a variety of spin traps. An easily determined spectral difference in the cyclized (16) vs. acyclic (15) adducts was established by labelling the 1-position of the 5-hexenyl radical with ^{13}C . The ^{13}C nucleus ($I=1/2$) causes hyperfine coupling in 15 but it is too far removed from the radical center in 16 to affect the esr signal. The fact that all the radicals are trapped is shown by



the agreement of the rate of decomposition of the peroxide with the rate of formation of the trap. By this method, it was determined that for NtB the ratio of trapping (k_t) to cyclization (k_c) is about 50 M^{-1} , and therefore k_t is $9.0 \times 10^7 \text{ M}^{-1}\text{sec}^{-1}$ at 40° in benzene. Rates were determined for several other spin traps at various temperatures by this method and/or a competition between two spin traps for the 1-hexenyl radical. Good agreement between the two methods was had in those cases where both methods were performed.

In order to determine the stabilities of the spin adducts once formed, or the rate at which the spin traps are destroyed, steady state measurements were made. The steady state kinetic equations assumed bimolecular self reactions and reactions with a second free radical to give O alkylation. The rate of disappearance of spin adducts is greatly dependent on the protection of the radical center and, in nitron adducts, on the crowding around the βH .

A number of general conclusions can be drawn from this study. For n-alkyl radicals, nitroso compounds trap faster than nitrones; e.g. for nitrosodurene (ND), $k_t = 3.9 \times 10^7 \text{ M}^{-1}\text{sec}^{-1}$ and for PBN, $k_t = 1.3 \times 10^5 \text{ M}^{-1}\text{sec}^{-1}$.

Aromatic nitroso compounds trap faster than alkyl nitroso compounds unless steric factors are great; e.g. NtB vs. ND. Aliphatic nitrones trap faster than aromatic nitrones; e.g. methylene-N-t-butylitrone, $k_t = 3.1 \times 10^6$, vs. PBN. Presumably the conjugation of the C=N bond with the ring is destroyed in the transition state for addition. The rates for substituted PBN's correlate with σ^- -values giving ρ -values that are small but positive (0.2 ± 0.1) due to the weak nucleophilic nature of alkyl radicals.

The knowledge of the rate of formation and decomposition of spin traps can help remove the ambiguity that could be caused by minor side reactions involving free radicals in an otherwise non-radical reaction. For instance, anionic polymerization of styrene and several other olefins with n-BuLi as an initiator followed by addition of NtB gave a solution from which esr signals were obtained.²⁸ The spectrum was essentially the same as that from quenching a free radical initiated polymerization. Clearly, the bulk of the reaction follows the ionic mechanism, but the esr spin trapping technique is so sensitive that it can detect the minor portion that proceeds via an electron transfer mechanism. In this regard, the sensitivity of the technique is undesirable.

Summary. Spin trapping is a relatively new and promising technique for the study of short-lived free radicals. Much work still needs to be done, however, in order that the chemist may have a variety of spin traps to solve a particular problem.

BIBLIOGRAPHY

1. E. G. Janzen, *Accts. Chem. Res.*, 4, 31 (1971).
2. O. H. Griffith and A. S. Waggoner, *ibid.*, 2, 17 (1969); T. D. Lee and J. F. W. Keana, *J. Org. Chem.*, 43, 4226 (1978).
3. A. Terabe, K. Kuruma, and R. Konaka, *J. Chem. Soc., Perkin II*, 1252 (1973).
4. R. J. Holman and M. J. Perkins, *J. Chem. Soc., C*, 2324 (1971).
5. I. H. Leaner and G. C. Ramsey, *Tetrahedron*, 25, 5669 (1969).
6. J. W. Hartgerink, J. B. F. N. Engberts, Th. A. J. W. Wajer, and Th. J. DeBoer, *Rec. Trav. Chim., Pay-Bas*, 88, 481 (1969).
7. E. G. Janzen and B. J. Blackburn, *J. Am. Chem. Soc.*, 91, 4481 (1969).
8. E. G. Janzen and B. J. Blackburn, *ibid.*, 90, 5909 (1968).
9. E. G. Janzen, *Accts. Chem. Res.*, 2, 279 (1969).
10. E. G. Janzen and J. D. P. Lui, *J. Mag. Res.*, 9, 510 (1973).
11. J. G. Pacific and H. L. Browning, Jr., *J. Am. Chem. Soc.*, 92, 5231 (1970).
12. C. M. Carmaggi and M. J. Perkins, *J. Chem. Soc., Perkin II*, 507 (1972).
13. A. Terabe and R. Kanaka, *ibid.*, 369 (1973).
14. J. R. Harbour and J. R. Bolton, *Biochem. and Biophys. Res. Commun.*, 64, 803 (1975).
15. J. R. Harbour, V. Chow, and J. R. Bolton, *Can. J. Chem.*, 52, 3549 (1974).
16. G. R. Chalfont, M. J. Perkins, and A. Horsfield, *J. Chem. Soc.*, 401 (1970).
17. E. G. Janzen, B. R. Knauer, L. T. Williams, and W. B. Harrison, *J. Phys. Chem.*, 74, 3025 (1970).
18. A. J. Bard, J. C. Gilbert, and R. D. Goodin, *J. Am. Chem. Soc.*, 96, 620 (1974).
19. A. L. F. Beckwith and R. O. C. Norman, *J. Chem. Soc., B*, 403 (1969).

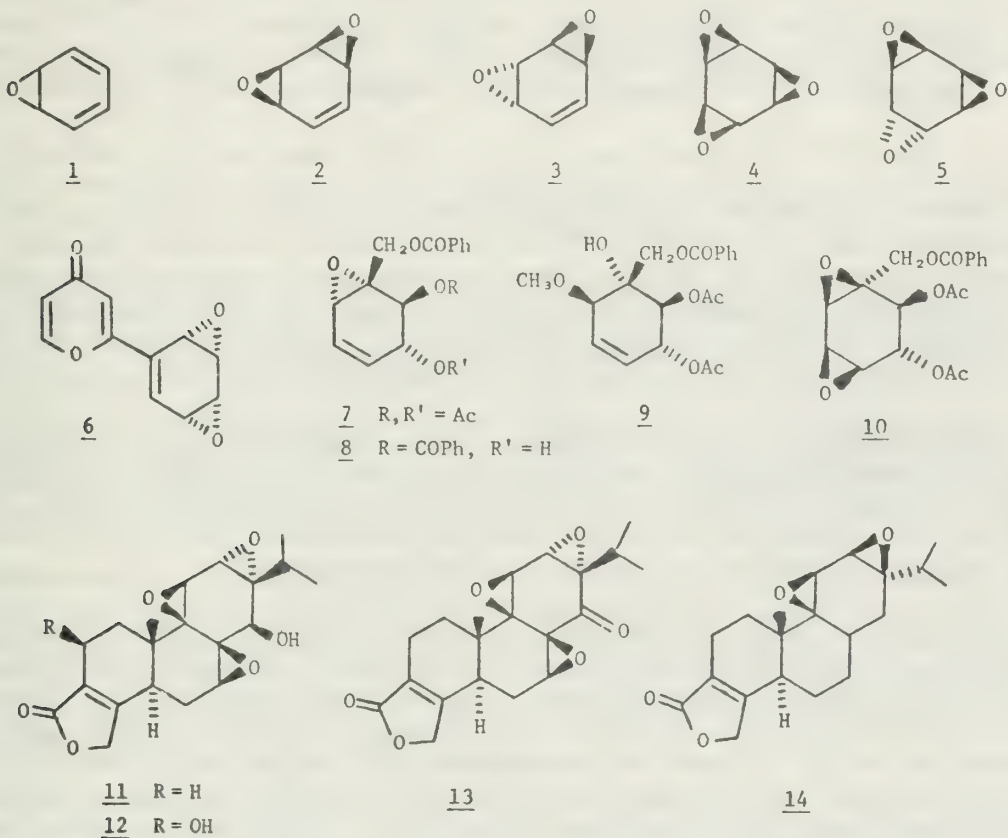
20. E. G. Janzen and I. G. Lopp, J. Phys. Chem., 76 (1972).
21. M. V. George and K. S. Balachandran, Chem. Rev., 75, 491 (1975).
22. S. Terabe and R. Kanaka, J. Chem. Soc., Perkin II, 2163 (1972).
23. P. H. Kasai and D. McLeod, Jr., J. Phys. Chem., 82, 619 (1978)
24. E. G. Janzen, C. A. Evans, and Y. Nishi, J. Am. Chem. Soc., 94, 8236 (1972).
25. P. Schmid and K. U. Ingold, J. Am. Chem. Soc., 100, 2493 (1978).
26. D. Lal, D. Griller, S. Husband, and K. U. Ingold, *ibid.*, 96, 6355 (1974).
27. C. Walling, J. H. Cooley, A. A. Panares, and E. J. Racak, *ibid.*, 88, 5361 (1966); C. Walling and A. Ciaffari, *ibid.*, 94, 6059 (1972).
28. A. R. Forrester and S. P. Hepburn, J. Chem. Soc., C, 701 (1971).
29. Note added in proof: E. G. Janzen *et al.* have recently taken issue with the assignment of structure 11 from reference 23 by Kasai and McLeod. See E. G. Janzen, R. C. Dudley, E. R. Davis, and C. A. Evans, J. Phys. Chem., 82, 2445 (1978).

BENZENE DIOXIDE, TRIOXIDE AND THE RELATED NATURAL PRODUCTS

Reported by Steven J. Hobbs

December 7, 1978

There are five possible benzene oxides: benzene oxide (1), the syn- and anti-benzene dioxides (2) and (3), respectively, and finally the syn- and anti-benzene trioxides (4) and (5). These various oxides of benzene have been the subjects of much research owing to: 1) their potential intermediacy in the metabolism of aromatic compounds; 2) the possibility of "crown ether" complexations with cations; 3) their potential valence isomerizations to novel heterocycles; 4) their possible value in the regiospecific synthesis of cyclohexane derivatives; and 5) their structural relationships to the natural products LL-Z1220 (6), senepoxide (7), pipoxide (8), seneol (9), and crotepoxide (10), as well as to the diterpenes: triptolide (11), triptidiolide (12), triptonide (13), and stemolide (14). This abstract will review the research encompassing the higher oxides of benzene (2 - 5) and the structurally related natural products (6 - 14).

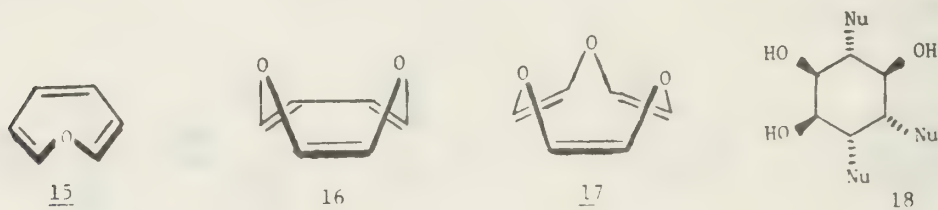


The biological significance of benzene oxides, their chemistry and syntheses have been the subject of several reviews.¹⁻⁴ Briefly, benzene oxides may undergo the NIH shift^{1,2} and may tautomerize to the corresponding oxepin via formally a $\pi^2s + \pi^2s + \sigma^2s$ cycloreversion.³ In addition, benzene oxides undergo attack by various nucleophiles to form a variety of products.²

Both the syn⁵ and the anti⁶ isomers of benzene dioxide (2 and 3, respectively) have been synthesized to date. The most efficient synthesis of the syn isomer at present is that of Vogel in low overall yield starting from 1,4-cyclohexadiene monoepoxide.^{5b}

A greater number of syntheses have appeared for anti-benzene dioxide (3).⁶ A recent, highly efficient synthesis of 3 starting from p-benzoquinone by Vogel has made anti-benzene dioxide (3) more readily available for study.^{6c}

Both syn- and anti-benzene dioxide are crystalline solids. While the syn isomer is stable for some time at room temperature,^{5b} 3 suffers relatively rapid decomposition.^{6a} In addition, 2 formally undergoes the $\pi^2s + \sigma^2s + \sigma^2s$ cycloreversion to the valence tautomer 1,4-dioxocin (16) rapidly in benzene heated above 50°C.^{5b} In contrast, benzene oxide (1) and oxepin (15) equilibrate rapidly at room temperature to provide comparable amounts of the two components.³ However, the anti isomer (3), when heated to 150°C in benzene, does not give 16.^{6a} Studies of the behavior of the benzene dioxides towards nucleophiles have been confined to the syn isomer (2).⁷



Several syntheses exist for syn-benzene trioxide (4)⁸ and anti-benzene trioxide (5).^{9,6b,6c,8a} For syn-benzene trioxide the most efficient synthesis to date is that of Prinzbach, starting from 1,4-cyclohexadiene monoepoxide.^{8b} A wider variety of syntheses exist for the anti-isomer (5). A facile synthesis of 5 from p-benzoquinone has recently been reported by Vogel and co-workers.^{6c}

The structures of the isomeric benzene trioxides (4 and 5) rest on chemical transformations, spectral data, and, in the case of 4, x-ray crystallography.^{8,9a,10} As in the case of the benzene dioxides, the trioxides are crystalline solids, the syn-trioxide (4) having an unusually high melting point for a compound of its structure.^{8a}

The syn trioxide (4) formally undergoes the $\sigma^2s + \sigma^2s + \sigma^2s$ cycloreversion to the all cis-trioxonin (17) at 200°C in acetonitrile. The reaction is in sharp contrast to the syn-benzene dioxide (2). However, the anti-trioxide (5), even with gas phase pyrolysis at 500°C does not tautomerize to 17. Vogel has suggested that the apparent inability of the anti-dioxide (3) and anti-trioxide (5) to tautomerize to 16 and 17, respectively, may be due to steric factors.^{8a} The thermal isomerization of the syn isomer (4) to 17 has been studied in detail by Penny and the activation energy and entropy for the process have been determined. On the basis of these values, Penny has suggested that the process is indeed a concerted one.¹¹

When the syn trioxide (4) is allowed to react with excess monovalent nucleophiles under neutral, basic or acidic conditions, regiospecific trisubstitution produces products of the chiro-inositol structure (18). With divalent nucleophiles, 4 yields substituted products with regiospecificity as well.¹³ These regiospecific substitutions have been employed in efficient syntheses of streptamine,¹⁴ syn-benzene triimine,¹⁵ syn-benzene trisulfide¹⁶ and other triheterotris- σ -homobenzenes.¹⁷

There are several natural products related to the dioxides (2) or (3), namely LL-Zl220 (6), senepoxide (7), and pipoxide (8). Although 6 is a substituted benzene dioxide itself, 7 and 8 could be derived via ring opening of a benzene dioxide derivative.

The antibiotic LL-Zl220 (6) is an optically active, stable solid, active *in vitro* against gram positive and gram negative bacteria. However, 6 is ineffective *in vivo*.^{18a} The structure of 6 rests on chemical transformations and spectral data.^{18b,c} Interestingly, in hot acetic anhydride, LL-Zl220 (6) gives the valence tautomer analogous to 11.^{18c}

Senepoxide and seneol, 7 and 9, respectively, have been isolated from the plant genus *Uvaria*.^{19a} Their structures have been assigned via chemical evidence and spectral data, while the absolute configuration assigned via ORD data,^{19a} and, in the case of 7, X-ray crystallography.^{19b}

Two syntheses of senepoxide (7) exist in the literature. One, of the syntheses by Ichihara and co-workers, employs a novel Diels-Alder cycloaddition of a fulvene derivative to insure stereoselectivity in the synthesis.^{20a} Ganem has prepared senepoxide (7) and seneol (9) by a novel "biomimetic" route which, in a key step, involves the formation of a derivative of benzene oxide (1).^{20b,c}

Pipoxide (8) has been isolated from the plant genus *Piper*. At this time, its absolute configuration is not known, but the general structure is based on chemical and spectral evidence.²¹

Crotopoxide (10) is related to benzene trioxide via formally a ring opening of one of the epoxide groups of a corresponding derivative of 4 or 5. This anti-tumor compound has been isolated from a number of plant families.²² The structure of crotopoxide (10) is based most definitively on the X-ray crystallographic work of the Kupchan group.^{22b} Crotopoxide has been synthesized by Ichihara using a similar approach to that used for senepoxide.^{23a} More recently, J. D. White and co-workers have prepared crotopoxide starting from a 1,4-dihydrobenzene derivative.^{23b}

According to Ganem, the biogenesis of crotopoxide (10), senepoxide (7), and pipoxide (8) may proceed through a benzene oxide (1) derivative produced from isochorismic acid. Photooxygenation of the benzene oxide derivative leads eventually to crotopoxide (10), while monoepoxidation of the benzene oxide derivative to a benzene dioxide could account for senepoxide (7) and pipoxide (8).²⁴

Triptolide (11), triptidiolide (12), triptonide (13),²⁵ and stemolide (14)²⁶ are novel diterpenes of the novel 18(4→3) abeo-abietane structure as verified by spectral data and X-ray crystallography.^{25,26} Two members of this novel family of compounds are anti-leukemic, namely 11 and 12.²⁷ Compounds 11-14 possess the basic 1,3-cyclohexadiene diepoxide structure of crotopoxide. Synthetic studies of the triptolides are currently being carried out by the Berchtold group.²⁸

BIBLIOGRAPHY

1. (a) J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, 28, 1129 (1972); (b) D. M. Jerina and J. W. Daly, *Science*, 185, 573 (1974).
2. D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, 1, 267 (1973).

3. E. Vogel and H. Gunther, *Angew. Chem. Int. Ed.*, 6, 385 (1967).
4. R. Amos, University of Illinois Organic Chemistry Seminar Abstracts, Semester II (Spring), 1974-75, p. 120.
5. (a) E. Vogel, H. J. Altenbach, and D. Cremer, *Angew. Chem. Int. Ed.*, 11, 935 (1972); (b) H. J. Altenbach and E. Vogel, *ibid.*, 11, 937 (1972).
6. (a) E. Vogel, H. J. Altenbach, and E. Schmidbauer, *Angew. Chem. Int. Ed.*, 12, 838 (1973); (b) C. H. Foster and G. A. Berchtold, *J. Org. Chem.*, 40, 3743 (1975); (c) H. J. Altenbach, H. Stegelmeier, and E. Vogel, *Tetrahedron Lett.*, 36, 3333 (1978).
7. E. Vogel, E. Schmidbauer and H. J. Altenbach, *Angew. Chem.*, 86, 818 (1974).
8. (a) E. Vogel, H. J. Altenbach, and C. D. Sommerfeld, *Angew. Chem. Int. Ed.*, 11, 939 (1972); (b) R. Schwesinger and H. Prinzbach, *ibid.*, 11, 942 (1972).
9. (a) C. H. Foster and G. A. Berchtold, *J. Am. Chem. Soc.*, 94, 7939 (1972); (b) H. Prinzbach, R. Keller, and R. Schwesinger, *Angew. Chem. Int. Ed.*, 14, 633 (1975); (c) H. Prinzbach and H. W. Schneider, *Tetrahedron Lett.*, 35, 3073 (1975).
10. W. Littke and U. Druck, *Angew. Chem.*, 86, 557 (1974).
11. D. E. Penny, *J. Chem. Soc., Perkin II*, 36 (1976).
12. (a) R. Schwesinger, H. Fritz, and H. Prinzbach, *Angew. Chem. Int. Ed.*, 12, 993 (1973); (b) L. Knothe and H. Prinzbach, *Tetrahedron Lett.*, 15, 1319 (1975).
13. R. Schwesinger, H. Fritz, and H. Prinzbach, *Angew. Chem. Int. Ed.*, 12, 994 (1973).
14. R. Schwesinger and H. Prinzbach, *Angew. Chem. Int. Ed.*, 14, 630 (1975).
15. R. Schwesinger and H. Prinzbach, *ibid.*, 12, 989 (1973).
16. S. Kagabu and H. Prinzbach, *Angew. Chem. Int. Ed.*, 14, 252 (1975).
17. H. Prinzbach, C. Kaiser, and H. Fritz, *ibid.*, 14, 253 (1975).
18. (a) D. Borders, F. Barbatschi, A. J. Shay, and P. Shu, *Antimicrob. Ag. Chemother.*, 233 (1969); (b) D. B. Borders, P. Shu, and J. E. Lancaster, *J. Am. Chem. Soc.*, 94, 2540 (1972); (c) D. B. Borders and J. E. Lancaster, *J. Org. Chem.*, 39, 435 (1974).
19. (a) R. Hollands, D. Becher, A. Gaudemer, and J. Polonsky, *Tetrahedron*, 24, 1633 (1968); (b) A. Ducruix, C. Pascaro, and J. Polonsky, *Acta Cryst.*, 32, 1589 (1976).
20. (a) A. Ichihara, K. Oda, M. Kobayashi, and S. Sakamura, *Tetrahedron Lett.*, 4235 (1974); (b) G. W. Holbert and B. Ganem, *J. Am. Chem. Soc.*, 100, 352 (1978); (c) B. Ganem, G. W. Holbert, L. B. Weiss, and K. Ishizumi, *ibid.*, 100, 6483 (1978).
21. J. Singh, K. L. Dhar, and C. K. Atal, *Tetrahedron*, 26, 4403 (1970).
22. (a) S. M. Kupchan, R. J. Hemingway, P. Coggon, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, 90, 2982 (1968); (b) S. M. Kupchan, R. J. Hemingway, and R. M. Smith, *J. Org. Chem.*, 34, 3899 (1969); (c) S. Takahashi, *Chem. Pharm. Bull.*, 18, 199 (1970); (d) S. Takahashi, *Phytochemistry*, 8, 321 (1969); (e) J. Singh, K. L. Dhar, and C. K. Atal, *Curr. Sci.*, 38, 471 (1969); (f) J. Singh and C. K. Atal, *Indian J. Pharm.*, 31, 129 (1969).
23. (a) K. Oda, A. Ichihara, and S. Sakamura, *Tetrahedron Lett.*, 37, 3187 (1975); (b) M. R. Demuth, P. E. Garrett, and J. D. White, *J. Am. Chem. Soc.*, 98, 634 (1976).
24. B. Ganem and G. W. Holbert, *Bioorganic Chem.*, 6, 393 (1977).
25. (a) S. M. Kupchan, W. A. Court, R. G. Daley, Jr., C. J. Gilmore, and R. F. Bryan, *J. Am. Chem. Soc.*, 94, 7194 (1972); (b) C. J. Gilmore and R. F. Bryan, *J. Chem. Soc., Perkin II*, 816 (1972).

26. P. S. Manchand and J. F. Blount, *Tetrahedron Lett.*, 2489 (1976).
27. S. M. Kupchan and R. M. Schubert, *Science*, 185, 791 (1974).
28. F. T. Sher and G. A. Berchtold, *J. Org. Chem.*, 42, 2569 (1977).

RECENT SYNTHETIC METHODOLOGY FOR FLUORINATION OF AROMATIC COMPOUNDS: APPLICATION IN ¹⁸F LABELLING

Reported by John S. Ng

December 11, 1978

One of the most rapidly developing fields of organic chemistry in recent years is the area of organic fluorine chemistry. The changes in the chemical reactivity and properties caused by introduction of fluorine into organic compounds have been recognized by organic chemists in the use of fluorinated substituents as labels or probes, as controlling substituents for mechanistic studies, or as activators of a chemical or biological property. More recently, research has been directed towards the preparation of radiopharmaceuticals incorporating the radionuclide ¹⁸F. Such compounds have significant potential applications in nuclear medicine.¹ For example, fluorine-18 labelled estrogen analogs have also been designed as potential breast tumor localizing agents.²

Despite the fact that direct aromatic chlorinations and brominations can easily be achieved through electrophilic substitution in the presence of a Lewis acid catalyst, direct fluorination is hazardous and usually results in extensive skeletal fragmentation of the organic molecule.³ Recently, improved direct fluorination with careful control of the exothermicity by molecular sieves has been developed with limited success.^{4,5}

The pyrolysis of diazonium fluoroborate, the Balz-Schieman reaction, remains the most generally used means of introducing fluorine into an aromatic ring. Recently, the reaction has been modified by employing photolysis,^{6,7} or crown-ether-copper-catalyzed decompositions of the diazonium salt.^{8,9} A similar reaction using the decomposition of fluoroformates has also been used to prepare certain aryl fluorides.¹⁰⁻¹²

A number of new fluorinating agents have been developed during the past decade. One of the more promising is xenon difluoride, which has been shown to successfully fluorinate a wide variety of aromatic compounds¹³⁻¹⁸ including estrone-3-methyl ether.¹⁹ This reagent has great potential value as it tolerates many active functions like hydroxy and amino groups.¹³ Trifluoromethylhypofluorite has also been used to introduce fluorine into a few aromatic systems with some success.²⁰⁻²⁶

Nucleophilic substitution reactions remain an interesting alternative to aromatic fluorination. Efforts have been made in fluorodenitration²⁷⁻³⁰ and halogen-exchange reactions.³¹⁻³³

Other novel approaches have been developed in the aromatic fluorination of specific systems. Anhydrous hydrogen fluoride has been found to react with phenylhydroxylamines³⁴⁻³⁶ or azides³⁷ to produce the corresponding p-fluoroanilines. Taylor and McKillop succeeded in fluorinating some aromatics through arylthallium difluoride intermediates.³² Electrolytic methods have also been investigated as an alternative to aromatic fluorination with limited success.³⁹ Fluorination of an olefinic precursor followed by aromatization represents yet another interesting approach to aromatic fluorination.⁴⁰

Despite the diverse methods available for aromatic fluorination, none of these are well-suited to introduce fluorine-18 into aromatic systems. Xenon difluoride and trifluoromethylhypofluorite are not easily available

in radioactive form. The methods with anhydrous hydrogen fluoride or thallium difluoride are useful only in specific systems. Nucleophilic substitution reactions appear promising but very strong electron withdrawing groups in the ring are necessary for success. The Bals-Schieman reaction is most commonly used although it is inefficient. A maximum of 25% of the fluorine-18 activity added can become organic bound from interchange with the tetrafluoroborate counterion. Furthermore, the fluoroborate counterion is usually employed in vast excess over the amount of fluorine added as fluorine-18, so the dilution of specific activity of fluorine-18 is usually enormous.

To solve these problems a number of novel approaches to devise new synthetic methodology that will be better suited for introducing fluorine-18 into aromatic systems have been undertaken and will be discussed.

BIBLIOGRAPHY

1. G. D. Robinson, "Radiopharmaceuticals", Soc. Nucl. Med., New York, 1975, p. 141.
2. Kurt W. Raack, M. S. Thesis of Chemistry, University of Illinois, 1978.
3. H. Moissan, Compt. Rend., 140, 407 (1905).
4. V. Grakauskas, J. Org. Chem., 35, 723 (1970).
5. Sams Lewis, *ibid.*, 43, 2273 (1978).
6. K. L. Kirk, *ibid.*, 41, 2373 (1976).
7. R. C. Petterson, *ibid.*, 36, 631 (1971).
8. G. D. Hartman and S. E. Biffar, *ibid.*, 42, 1468 (1977).
9. E. D. Bergmann and S. Berkovic, *ibid.*, 20, 919 (1960).
10. K. O. Christe and A. E. Pavlath, *ibid.*, 30, 3170 (1965).
11. K. O. Christe and A. E. Pavlath, *ibid.*, 30, 4104 (1965).
12. K. O. Christe and A. E. Pavlath, *ibid.*, 31, 559 (1966).
13. Robert Filler, Israel J. of Chem., 17, 71 (1978).
14. Robert Filler, J. Org. Chem., 40, 3797 (1975).
15. Robert Filler and M. J. Shaw, J. Am. Chem. Soc., 91, 1563 (1969).
16. Robert Filler and M. J. Shaw, *ibid.*, 92, 6498 (1970).
17. Marko Zupan and Alfred Pollak, J. Org. Chem., 40, 3795 (1975).
18. H. H. Hyman and R. Filler, *ibid.*, 40, 807 (1975).
19. R. Filler and L. Quarterman, Abs. Pap. Amer. Chem. Soc., 170, 14 (1975).
20. J. Kollonitsch, Israel J. of Chem., 17, 53 (1978).
21. J. Kollonitsch and L. Barash, J. Am. Chem. Soc., 98, 5591 (1976).
22. T. B. Patrick, J. Org. Chem., 39, 2120 (1974).
23. Morris J. Robins, J. C. S. Chem. Commun., 18 (1972).
24. John A. Allison and George H. Cady, J. Am. Chem. Soc., 81, 1089 (1959).
25. J. Kollonitsch and L. Barash, J. Am. Chem. Soc., 92, 2494 (1970).
26. D. H. R. Barton and R. H. Hesse, Chem. Commun., 806 (1968).
27. G. Bartoli, J. Chem. Soc., Perkin Trans. I, 2671 (1972).
28. N. Ishikawa and T. Tanabe, Bull. Chem. Soc. Japan, 48, 359 (1975).
29. R. L. Markezich and F. J. Williams, J. Org. Chem., 42, 3435 (1977).
30. R. L. Markezich and O. S. Zamek, *ibid.*, 3431 (1977).
31. R. E. Banks, D. S. Field, and R. N. Hazeldine, J. Chem. Soc. (C), 1280 (1970).
32. G. C. Finger, R. H. Shiley, and D. R. Dickerson, J. Fluorine Chem., 4(1), 111 (1974).
33. R. N. Haszeldine, J. M. Birchall, and M. E. Jones, J. Chem. Soc. (C), 1341 (1971).

34. A. I. Titov and A. N. Baryshnikova, J. Gen. Chem., U.S.S.R., 23, 361 (1953).
35. T. B. Patrick, J. A. Schield, and D. G. Kirchner, J. Org. Chem., 39, 1758 (1974).
36. H. E. Heller, E. D. Hughes, and C. K. Ingold, Nature, 24, 909 (1951).
37. D. M. Mulrey, A. M. DeMarco, and L. M. Weinstock, Tetrahedron Lett., 16, 1419 (1978).
38. E. C. Taylor, E. C. Bigham, D. K. Johnson, and A. McKillop, J. Org. Chem., 42, 362 (1977).
39. I. N. Rozhnov, Dokl. Chem., 193, 618 (1970).
40. M. Neeman, J. Chem. Soc., Perkin I, 2300 (1972).

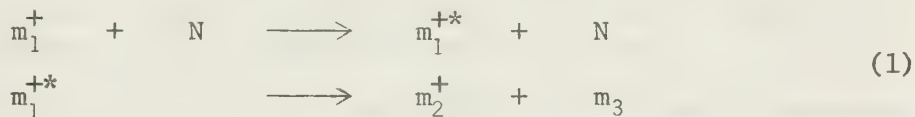
COLLISIONAL ACTIVATION MASS SPECTROMETRY

Reported by Chuck Snelling

December 12, 1978

Mass spectroscopists have known of collisionally-induced processes for over fifty years.^{1,2} The collisionally-induced dissociation of an ion involving a residual gas in the mass spectrometer was considered annoying because of the spurious results obtained in metastable studies. However, in the last decade, mainly through the efforts of McLafferty,^{3,4} Levsen,^{5,6} Jennings,⁷ Cooks,⁸ and Beynon,^{9,10} it has been discovered that these processes can provide a wealth of information on the physical structure and reactivity of gas-phase ions.

Collisionally-induced decompositions (CID), or collisional activation (CA), refers to a process by which stable ions having high translational energy are allowed to experience an inelastic collision with small, neutral atoms or molecules in the mass spectrometer. When an ion having a translational energy of 1Kev or more collides, inelastically, with a target gas, part of the ion's translational energy is converted into electronic excitation. The electronic excitation is then quickly converted to vibrational energy which distributes itself statistically throughout the ion.¹¹ This "collisionally activated" ion then decomposes into a daughter ion and a neutral fragment:



The translational energy the ion loses on collision is on the same order as that it gains in electronic excitation; the amount of energy transferred to the target atoms is negligible.¹² Thus the amount of energy necessary to excite an ion into a given electronic state can easily be measured by the loss of its translational energy. The subsequent dissociation of the excited ion into a secondary ion and a neutral fragment is accomplished with a release of translational energy. This translational or "non-fixed" energy represents the excess energy that the ion possesses above what is necessary to overcome the barrier to dissociation. Thus, it can be seen that a CA spectrum can provide information about the relative intensities and masses of secondary ions, the excitation energy of the ion and the translational energy released on dissociation.

Determination of the excitation energy as well as the energy released on dissociation provides valuable insights into the thermochemical properties of an ion. Cooks, et al.,¹² have made detailed studies for a series of aliphatic alcohols on the uses of these energies in predicting the stability of product ions and the electronic states in which the collisionally induced fragments are formed. They found that for methanol and ethanol, CA allowed definition of the energy partitioning of an ion's non-fixed energies. They also found that CA allowed for more detailed study of breakdown curves at high energies because more reaction pathways could be studied than those available for metastable ions.

McLafferty³ has studied several of the parameters affecting the intensity ratios of a CA spectrum and has found that the relative abundances of product ions is first order in collision gas in the range

of 10^{-3} Torr. Below 10^{-4} Torr, the mean free path of an ion is equal to the length of the collision chamber and so no collisions occur. Above 5×10^{-4} Torr, however, there appears a positive deviation in this first order dependence on collision gas. This has been attributed to the fact that at this pressure there is a 60% chance of a second collision which leads to more efficient production of secondary ions.³

Both high target gas pressure and high accelerating potentials increase the relative abundance of ions having high appearance potentials.³ Table I shows the CA spectrum for the molecular ion of 1-propanol (m/e 60) at various target gas pressures and accelerating

Table I. Product Ion Abundance as a Function of Accelerating Potential (IA) and Target Gas Pressure.

IA, volts	Product Ion, m/e	Ion Abundance	
		1×10^{-4} Torr ^a	5×10^{-4} Torr ^a
450	59	21	-
	42	64	1
	31	15	-
1250	59	32	28
	42	46	35
	31	23	27
3750	59	32	21
	42	38	29
	31	30	50

^a Argon as the collision gas.

potentials. The relative abundance of the product ion with the highest appearance potential, CH_3O^+ (m/e 31), increases sharply with increased collision gas pressure. This increased ion abundance points to the need of ions with high appearance potentials to experience multiple collisions in order to acquire the necessary energy to overcome the barrier to dissociation. An analogous result is seen when the accelerating potential is increased for a given collision gas pressure. At higher accelerating potentials, an ion possesses a greater amount of kinetic energy that can be converted into internal energy on collision. Thus an ion with a high appearance potential has a better chance of experiencing a collisionally-induced dissociation at higher accelerating potentials.

McLafferty³ and other¹² have also investigated how the internal energy of the ion before collision affects the relative intensities of the product ions after collision. For some time it has been known that metastable ion (MI) spectra are very dependent on the internal energy of the decomposing ions. These ions can have internal energies ranging from just below the barrier to dissociation to several eV above it.³ CA, on the other hand, measures the properties of ions that are stable to decomposition in the absence of a collision gas. To show that CA is not dependent on the internal energy of an ion, McLafferty³ measured the ratio of secondary ion intensities relative to the parent ion at electron energies ranging from 12 to 50 eV. Although product ions with low appearance potentials did show some variations in the ratio of secondary ions to parent ion due to lower barriers to dissociation, the constant ratio obtained for secondary ions of higher appearance poten-

tials shows that a CA spectrum is, on the whole, very little, if at all, dependent on the internal energy of the parent ion before collision.

The final factor affecting the relative abundance of the product ions is the nature of the collision gas. Cooks, *et al.*,¹² have studied this effect and have shown that the nature of the collision gas has no influence on the intensity ratios and generally none on the excitation energy or translational energy released. The gas does, however, greatly affect the yield of the product ions. Table II shows the effect of collision gas on the reaction $(45)^+ \longrightarrow (28)^+$ for ethanol. The results are as expected; as the size of the atoms or molecules

Table II. Effect of Collision Gas on Various Parameters in a CA Spectrum.

Collision Gas	Q	T _{50%}	T _{base}	Abundance ^a
Air	4	0.11	0.38	0.3
He	3	0.11	0.37	0.4
H ₂	4	0.10	0.33	1.0
Xe	2	0.07	0.26	0.1

^aAbundances measured at 3×10^{-5} Torr.

decreases, the cross section and thus the yield increases. Because of this He and H₂ are particularly good target gases for CA although N₂ has been used because of its greater pumping efficiency.²

A CA spectrum is qualitatively very similar to a 70eV EI spectrum. Many have taken the view that this similarity strongly supports the major premise of the quasi-equilibrium theory,^{3,5,12,13} namely that no matter what form the excitation energy takes, an equilibrium is established so that this electronic excitation is distributed throughout all the allowed states of the ion in the form of vibrational energy. Since the pattern of bond breaking in an ion depends on the distribution of the ion's vibrational energy and not how this energy came about, an EI and CA spectrum should be very similar. In testing the similarity of bond breaking patterns using different modes of excitation, Jennings⁷ has shown that ions in a collision chamber not only undergo the same types of reactions that occur in an EI source, but also have the same resident times. McLafferty⁴ has pointed out a quantitative similarity for CA and EI spectra. He showed that CA spectra, like EI, are dominated by simple bond cleavages such as loss of methyl or ethyl radicals. These simple bond cleavages presumably occur via "loose" activated complexes where the ion does not need to fold or bend itself into a particular conformation for the cleavage to occur. However, the peaks in MI spectra are predominantly rearrangements which occur via "tight" activated complexes where the ion must assume a particular conformation in order for the rearrangement to occur. A variety of examples (Table III) show that (simple cleavages)/(rearrangements) values are at least an order of magnitude

Table III. Ratios of Simple Cleavages to Rearrangements for Reactions Occurring in the MI, CA, and EI Modes.

Compound	MI	CA	EI	Reaction Ratio
nitrobenzene	0.05	8	10	$(M-NO_2)^+ / (M-NO)^+$
phenylbutyrate	0.1	0.6	0.6	$(M-C_6H_5O)^+ / (M-C_4H_9O)^+$
triphenylcarbinol	0.1	1.4	4	$(M-C_6H_5)^+ / (M-C_7H_9O)^+$

or higher for CA relative to MI, and are very close to those found in EI. This similarity of bond cleavages in EI and CA has greatly facilitated the use of CA spectra in determining structures of secondary ions since the mechanisms used to explain bond cleavages in EI reactions can be directly transferred to the interpretation of CA bond cleavages.

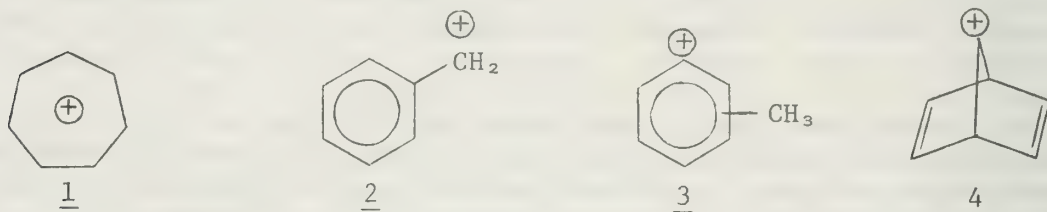
Most CA spectra are obtained by introduction of a collision gas into a collision chamber at the point where the ion beam is focused by the magnet,^{14,15} or by direct flooding¹¹ of the gas into the analyzing section of the mass spectrometer between the magnet and the electric sector. Other methods involve flooding¹⁶ the first field-free region and replacement of the collision gas with a surface as the activation medium.¹⁷

Prior to a CA measurement, a preliminary spectrum is taken in the absence of the collision gas. This spectrum represents the MI spectrum which is to be subtracted from the CA spectrum. After recording the MI spectrum, the magnet is adjusted to pass the ion of interest and the target gas pressure is increased so the intensity of the ion is attenuated by 10-30%. The electric sector is then scanned in a downward direction from 100-0% of its potential.¹⁸ This scan actually represents a kinetic energy spectrum of the ion, that is, a plot of the intensity of the secondary ion with a given kinetic energy vs. the strength of the electric field needed to bring the ion to focus at the detector. These values are readily converted to masses by relationship 2, where

$$m/e = Er_e / V^2 \quad (2)$$

m is the mass, E is the strength of the electric field, r_e is the radius of the electric sector, and V is the accelerating potential.

CA is the only mass spectrometric technique that allows the structure of ions to be directly determined. Since the ions undergo the same reactions as the parent compound, CA also has found extensive use in studies of reactive intermediates. For example, one of the most widely studied ions in organic mass spectrometry, the $C_7H_7^+$ ion, has been extensively studied by McLafferty¹⁹⁻²¹ by means of CA. Four isomers 1-4 have sufficiently long life times to have been characterized structurally. In this study, the CA spectra for the M-1 ion of cyclohepta-



triene was used as the prototype of the tropylium structure 1 (Table IV). Thus any ion having the same CA spectra was assumed to have the tropylium structure. The standard for the CA spectrum of the benzyl cation was obtained from 1,2 diphenylethane. Likewise, the CA standards for 3 and 4 were obtained from p-nitrotoluene and 2,5-norbornadiene, respectively.

Table IV. Standard CA Spectra for Structures 1-4.

Compound	m/e	Relative Abundance								% Benzyl
		39	41	50	51	63	74	75	76	77
Cycloheptatriene	24	4.5	11	19	31	2.0	2.6	2.2	3.7	20
Toluene	21	3.4	13	18	29	1.9	3.1	3.7	6.1	50
1,2 diphenylethane	22	4.8	10	18	28	2.1	2.2	3.6	9.7	90
p-nitrotoluene	22	5.3	13	17	31	4.0	3.4	2.8	1.4	
2,5-norbornadiene	24	4.3	11	19	29	2.3	2.8	2.5	3.8	25

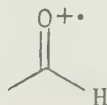
In the approximately sixty compounds studied, those with a $C_6H_5CH_2Y$ structure with $Y=H, OH, OCH_3$ exhibit the tropylium structure as the major product at m/e 91. These assignments were made due to similarity of these spectra to that of 1. However, no compound was found that had exclusively the tropylium structure. Moreover, the percentage of the benzyl cation 2 increased to as much as 90% as Y became CH_2Ph . Since there is a marked increase in the abundance of the benzyl cation as Y becomes Cl (45%), Br (50%), and I (65%), it is assumed that the major factors determining the percentage of the benzyl cation include how good a leaving group is attached to the $C_6H_5CH_2$ moiety and its ability to stabilize the radical.

Levsen has conducted CA studies of isomeric octanes,²² octenes and cycloalkanes²³ and found that the molecular ions retain their structural integrity while the alkyl fragments isomerize completely to a set of common fragments. He has proposed²⁴ that this behavior may best be explained by taking into account the possible radical character of the ions. If an ion has an even number of electrons, it is non-radical in character and the tendency towards isomerization is determined by the stability of the carbonium ion. However, if an ion has an odd number of electrons, it is a radical and thought to dissociate before isomerization. This behavior has been explained by the fact that the barrier to isomerization is thought to be higher than the barrier to dissociation for radical hydrocarbons. Levsen²⁵ has also found that the presence of a hetero atom greatly reduces the isomerization on non-radical type ions. This is probably due to the localization of the positive charge on the hetero atom. Other hydrocarbon ions of interest which have been studied by CA include: $C_8H_{16}^+$,²⁶ $C_4H_8^+$,²⁷ $C_6H_8^+$,²⁸ $C_5H_{10}^+$ and $C_6H_{12}^+$,²⁹ and $C_8H_9^+$.³⁰

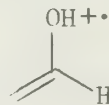
CA studies into the structure of various $C_2H_4X^+$ ions have been carried out for $X=O$,³¹ $X=CH_3$,³² $X=SH$,³³ and $X=N$.³⁴ For $X=O$, three isomers 5-7 were thought to be stable based on ground-state chemistry. As in previous studies, the standard CA spectra for 5-7 were obtained from ethylene oxide, acetaldehyde and n-butanal, respectively. For over thirty compounds studied, 5 was only seen to be formed from ethylene oxide and 1,3-dioxolane. Likewise, 6 was formed only from 1,3-



5



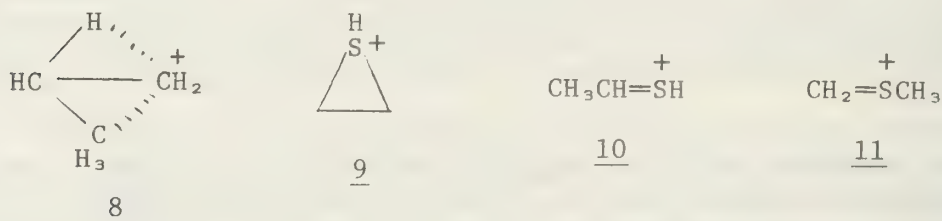
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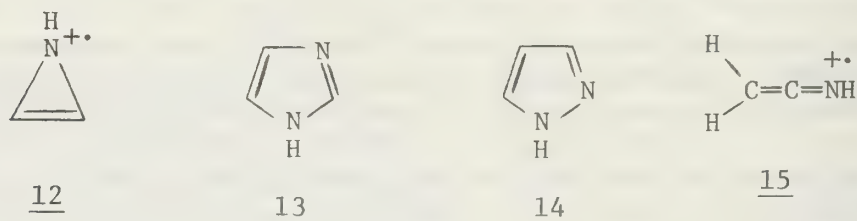
7

butanediol and its standard. Thus, structure 7, the enol form of the $C_2H_4O^+$ ion, was found to be the most stable form from precursors ranging from cyclic alcohols, vinyl ethers to halogenated alcohols.

For $X=CH_3$, the ion 8 seems to be the most stable structure. The sulfur analogue of 5, 9 has been detected and appears to be more stable



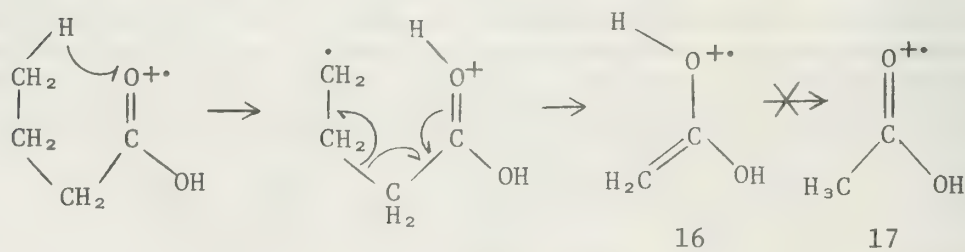
than 5, but again the linear structures 10 and 11 are formed preferentially and seem to point to the importance of good d-orbital overlap in sulfur for stabilization of the positive charge.³³ When $X=N$, the structure 12 is formed when the precursors imidazole (13) and pyrazole (14) are used. However, the linear structure 15 predominates when compounds containing the nitrile functionality are used. The $C_3H_6O^+$ ³⁵



and $C_3H_7S^+$ ³⁶ homologues of the above have been studied by CA and have analogous structures.

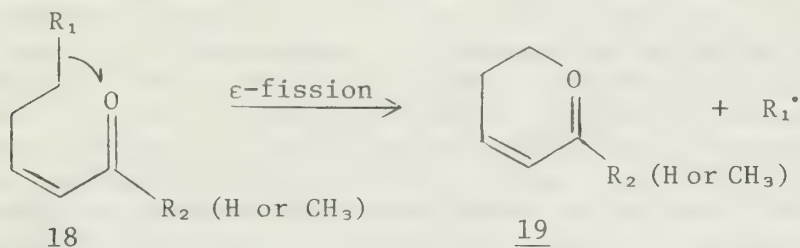
The structures of a number of oxygen containing compounds have been studied by CA.³⁷⁻⁴³ Levsen⁴⁴ has studied the structure of $C_2H_4O_2^+$ ions derived from the McLafferty rearrangement of aliphatic acids (Scheme I). He found through isotope labeling and comparison of the

Scheme I



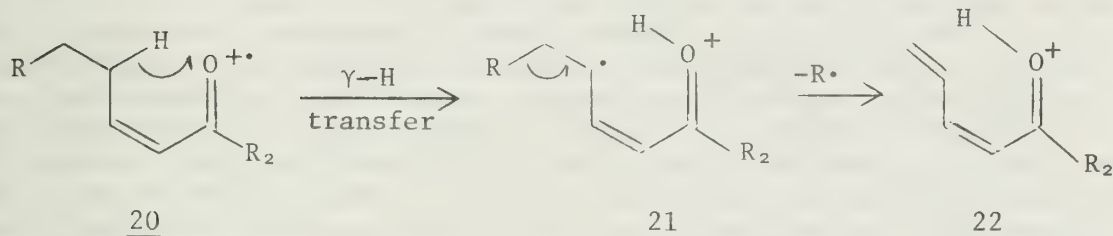
CA spectra of the $C_2H_4O_2^+$ ions with the CA spectra of authentic acetic acid, that the ion at m/e 60 indeed corresponded to 16 rather than to the molecular ion of acetic acid (17). In another study, the structure of the ions from α,β -unsaturated aldehydes and methyl ketones had been proposed by McLafferty⁴⁶ to occur by ϵ -fission (Scheme II).

Scheme II



Meyerson⁴⁷ challenged this mechanism immediately because he could see no special driving force for this unusual ϵ -fission. This controversy led Sande, *et al.*,⁴² to make a CA study of this reaction. They found that it actually occurs through well-established reactions (Scheme III).

Scheme III



Thus the structure of the ion at m/e 97 ($R_2=CH_3$) is 22 rather than 19 as proposed by McLafferty.

Other isolated systems have been studied by CA and include $C_2H_6N^+$ and $C_3H_8N^+$,⁴⁸ CH_3S^+ ,⁴⁹ and the formation of the tetramethylenechloronium ion in the gas phase.⁵⁰ CA methods have also been applied to investigate the structure of organic ammonium,⁵¹ phosphonium and sulphonium⁵² salts. In these studies, field desorption (FD) CA in conjunction with linked-scan techniques⁵³ provided sufficient fragmentation for structural elucidation of these salts where all other techniques had failed. FDCA has also been used with alkali metal ion attachment to differentiate the structures of several monosaccharides.⁵⁴ This has always been a very difficult problem for classical EIMS due to the low volatility of the sugar moiety. Thus this approach opens the possibility of studying other non-volatile natural products. With FDCA, alkali metal attachment to fragment ions as well as to the molecular ion has been seen for the first time.⁵⁵ Other modifications of the ionization modes for CA include negative chemical ionization⁵⁶ and negative electron impact.⁵⁷

The analytical applications of CA were apparent from its inception. Cooks⁵⁸ has shown that CA behaves in a similar or comparable fashion to GCMS, where CA uses the magnet as the GC and the electric sector as the MS. Most analytical techniques involving CA use the so-called soft ionization methods such as chemical ionization, field ionization and FD to reduce the complications brought about by fragment ions. Levsen and Schulten⁵⁹ have used EICA, with 14 eV electrons, to analyze the pyrolysis products of DNA directly with no sample preparation. Cooks, *et al.*,^{60,61} have investigated the mechanism for the methylation of ketones by directly introducing aliquots of the reaction mixture and carrying out CICA on methylation products. McLafferty⁶² has used CA for the detection of thiophene (<25 ppm), tetrahydropyran (<50 ppm), and n-propylbenzene (<500 ppm) in Exxon regular gasoline by direct sample introduction. Finally, the utility of CA in the structure determination of components of complex natural product mixtures has been investigated.^{63,64} One of the interesting applications in this respect is the identification of isomeric amino acids occurring in peptides. This is an old problem for mass spectroscopists interested in sequencing peptides because not even high resolution data will help. However, Levsen⁶⁴ has shown that if the ion at m/e 100, which is the immonium ion produced by decarboxylation of leucine and isoleucine, is analyzed by CA, the spectra are quite different and easily identifiable even when both are present in the peptide.

In summary, collisional activation mass spectrometry has been shown to be a very powerful tool in the study of gas-phase ions. For the physical chemist, the method allows probing the thermochemical properties of an ion using the excitation energy and the release of translational energy. For the natural products chemist, CA allows the structural determination of ions important to the overall structure of the parent natural product that was not possible before. For the analytical chemist, CA allows the direct analysis of complex mixtures with little or no sample preparation, eliminating a very common problem of producing artifacts by the separation technique used. Thus, it can be seen that CA covers a wide and useful spectrum of mass spectral techniques from theoretical ion energetics to analysis of mixtures that were very difficult, if not impossible, by other techniques.

BIBLIOGRAPHY

1. H. M. Rosenstock and C. E. Melton, *J. Chem. Phys.*, **26** (2), 314 (1957).
2. L. P. Hills, M. L. Vestal, and J. H. Futrell, *J. Chem. Phys.*, **54** (9), 3834 (1971).
3. F. W. McLafferty, P. F. Bente III, R. Kornfeld, Shih-Chuan Tsai, and I. Howe, *J. Am. Chem. Soc.*, **95**, 2120 (1973).
4. F. W. McLafferty, R. Kornfeld, W. F. Haddon, K. Levsen, I. Sakai, P. F. Bente III, Shih-Chuan Tsai, and H. D. R. Schuddemage, *J. Am. Chem. Soc.*, **95**, 3886 (1973).
5. K. Levsen and H. Schwarz, *Angew. Chem. Int. Ed. Engl.*, **15**, 509 (1976).
6. K. Levsen and H. D. Beckey, *Org. Mass Spec.*, **9**, 570 (1974).
7. K. R. Jennings, *Int. J. Mass Spect. and Ion Phys.*, **1**, 227 (1968).
8. J. H. Beynon and R. G. Cooks, *Int. J. Mass Spect. and Ion Phys.*, **12**, 107 (1974).

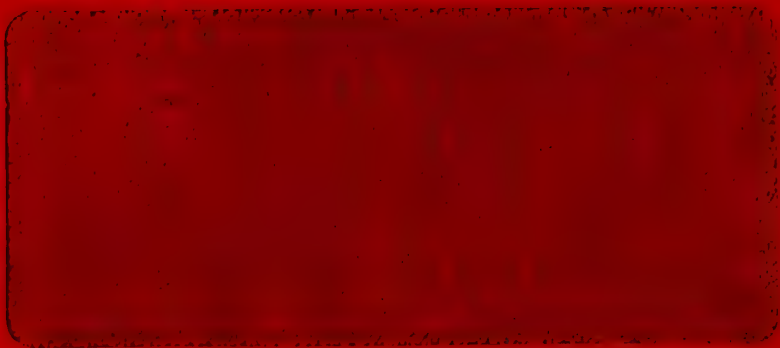
9. J. H. Beynon, R. G. Cooks, J. W. Amy, W. E. Baitinger, and T. Y. Ridley, *Anal. Chem.*, 45, 1023 (1973).
10. J. H. Beynon, R. M. Caprioli, W. E. Baitinger, and J. W. Amy, *Org. Mass Spec.*, 3, 479 (1970).
11. R. S. Stradling, K. R. Jennings, and S. Evans, *Org. Mass Spec.*, 13, 429 (1978).
12. R. G. Cooks, L. Hendricks, and J. H. Beynon, *Org. Mass Spec.*, 10, 625 (1975).
13. T. Wachs and F. W. McLafferty, *Int. J. Mass Spec. and Ion Phys.*, 23, 243 (1977).
14. T. Wachs, C. C. Van De Sande, P. F. Bente III, P. P. Dymerski, and F. W. McLafferty, *Int. J. Mass Spec. and Ion Phys.*, 23, 21 (1977).
15. T. Wachs, C. C. Van De Sande, and F. W. McLafferty, *Org. Mass Spec.*, 11, 1308 (1976).
16. R. Robbiani, T. Kuster, and J. Seib, *Angew. Chem. Int. Ed. Engl.*, 16, 120 (1977).
17. R. G. Cooks, D. T. Terwilliger, T. Ast, J. H. Beynon, and T. Keough, *J. Am. Chem. Soc.*, 97, 1583 (1975).
18. A. F. Weston, K. R. Jennings, S. Evans, and R. M. Elliot, *Int. J. Mass Spec. and Ion Phys.*, 20, 317 (1976).
19. J. Winkler and F. W. McLafferty, *J. Am. Chem. Soc.*, 95, 7533 (1973).
20. F. W. McLafferty and J. Winkler, *J. Am. Chem. Soc.*, 96, 5186 (1974).
21. K. Levsen, F. W. McLafferty, and D. M. Jerima, *J. Am. Chem. Soc.*, 95, 6332 (1973).
22. K. Levsen, *Org. Mass Spec.*, 10, 43 (1975).
23. K. Levsen, *Org. Mass Spec.*, 10, 55 (1975).
24. K. Levsen and J. Heimbrecht, *Org. Mass Spec.*, 12, 131 (1977).
25. K. Levsen, *Tetrahedron*, 31, 2431 (1975).
26. F. Borchers, K. Levsen, H. Schwarz, C. Wesdemiotis, and R. Wolfshutz, *J. Am. Chem. Soc.*, 99, 1716 (1977).
27. T. Nishishita, F. M. Bockhoff, and F. W. McLafferty, *Org. Mass Spec.*, 12, 16 (1977).
28. T. E. Smith, S. R. Smith, and F. W. McLafferty, *Org. Mass Spec.*, 13, 254 (1978).
29. T. Nishishita and F. W. McLafferty, *Org. Mass Spec.*, 12, 75 (1977).
30. C. Koppel, C. C. Van De Sande, N. M. M. Nibbering, T. Nishishita, and F. W. McLafferty, *J. Am. Chem. Soc.*, 99, 2883 (1977).
31. C. C. Van De Sande and F. W. McLafferty, *J. Am. Chem. Soc.*, 97, 4613 (1975).
32. P. P. Dymerski, R. M. Prinstein, P. F. Bente III, and F. W. McLafferty, *J. Am. Chem. Soc.*, 98, 6834 (1976).
33. B. Van De Graaf and F. W. McLafferty, *J. Am. Chem. Soc.*, 99, 6806 (1977).
34. J. Van Thuijl, J. J. Van Houte, A. Maquestiau, R. Flammang, and C. De Meyer, *Org. Mass Spec.*, 12, 196 (1977).
35. C. C. Van De Sande and F. W. McLafferty, *J. Am. Chem. Soc.*, 97, 4617 (1975).
36. B. Van De Graaf and F. W. McLafferty, *J. Am. Chem. Soc.*, 99, 6810 (1977).
37. A. Maquestiau, Y. Van Haverbeke, R. Flammang, C. De Meyer, K. G. Das, and G. S. Reddy, *Org. Mass Spec.*, 10, 631 (1977).
38. F. Borchers, K. Levsen, C. B. Theissling, and N. M. M. Nibbering, *Org. Mass Spec.*, 12, 746 (1977).
39. D. J. McAdoo, D. N. Witiak, F. W. McLafferty, and J. D. Dill, *J. Am. Chem. Soc.*, 100, 6639 (1978).

40. F. W. McLafferty and K. Sakai, *Org. Mass Spec.*, 7, 971 (1973).
41. N. M. M. Nibbering, C. C. Van De Sande, T. Nishishita, and F. W. McLafferty, *Org. Mass Spec.*, 9, 1059 (1974).
42. C. C. Van De Sande, C. De Meyer, and A. Maquestiau, *Bull. Soc. Chim. Belg.*, 85, 79 (1976).
43. K. Levsen and F. W. McLafferty, *Org. Mass Spec.*, 8, 353 (1974).
44. K. Levsen and H. Schwarz, *J. Chem. Soc., Perkin II*, , 1231 (1976).
45. F. W. McLafferty, "Mass Spectrometry of Organic Ions," F. W. McLafferty, ed., Academic Press, New York, 1963, chapter 7.
46. S. Meyerson, *Int. J. Mass Spec. and Ion Phys.*, 1, 309 (1968).
47. K. Levsen and F. W. McLafferty, *J. Am. Chem. Soc.*, 96, 139 (1974).
48. J. D. Dill and F. W. McLafferty, *J. Am. Chem. Soc.*, 100, 2907 (1978).
49. C. C. Van De Sande and F. W. McLafferty, *J. Am. Chem. Soc.*, 97, 2298 (1975).
50. H. J. Veith, *Org. Mass Spec.*, 13, 280 (1978).
51. H. H. Gierlich, F. W. Rollgen, F. Borchers, and K. Levsen, *Org. Mass Spec.*, 12, 387 (1977).
52. D. L. Kemp, R. G. Cooks, and J. H. Beynon, *Int. J. Mass Spec. and Ion Phys.*, 20, 317 (1976).
53. F. W. Rollgen, U. Giessmann, F. Borchers, and K. Levsen, *Org. Mass Spec.*, 13, 459 (1978).
54. F. W. Rollgen, F. Borchers, U. Giessmann, and K. Levsen, *Org. Mass Spec.*, 12, 541 (1977).
55. F. J. Winkler and D. Stahl, *J. Am. Chem. Soc.*, 100, 6779 (1978).
56. J. H. Bowie, P. Y. White, J. C. Wilson, F. C. V. Larsson, S. O. Lawesson, J. O. Madsen, C. Nolde, and G. Schroll, *Org. Mass Spec.*, 12, 191 (1977).
57. R. W. Kondrat and R. G. Cooks, *Anal. Chem.*, 50, 81 (1978).
58. K. Levsen and H.-R. Schulten, *Biomed. Mass Spec.*, 3, 137 (1976).
59. L. Kruger, J. F. Litton, R. W. Kondrat and R. G. Cooks, *Anal. Chem.*, 48, 2113 (1976).
60. T. L. Kruger, J. F. Litton, and R. G. Cooks, *Anal. Let.*, 9, 533 (1976).
61. F. W. McLafferty and F. M. Bockhoff, *Anal. Chem.*, 50, 89 (1978).
62. K. Levsen, H.-K. Wipf, and F. W. McLafferty, *Org. Mass Spec.*, 8, 117 (1974).
63. A. Maquestiau, Y. Van Haverbeke, R. Flammang, H. Mispereuve, M. Kaisin, J. C. Braekman, D. Daloze, and B. Tursch, *Steroids*, 31, 31 (1978).

ORGANIC SEMINAR ABSTRACTS

1978-79, Semester II

University of Illinois



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CHEMICAL IONIZATION MASS SPECTROMETRY

Reported by Moustapha E. Koker

January 25, 1979

Chemical ionization (CI) mass spectrometry dates from the observation of Field and Munson that an ion such as CH_5^+ can ionize sample molecules by transferring a proton to them in the gas phase.¹ Such an ionization process is different from ionization methods used in other mass spectrometric techniques.²⁻⁴ In CI mass spectrometry a set of reagent ions is first generated by bombarding a suitable reagent gas at a relatively high pressure with high energy electrons. These react with sample molecules mainly by ion-molecule reactions and produce ions characteristic of the unknown sample.

In addition to being an efficient technique for the production of a wide variety of positive ions, CI is also a superb method for the generation of negatively charged sample ions. Because of the large concentration of thermal or near thermal energy electrons produced during ionization of the CI reagent gas, the resonance electron capture mechanism operates efficiently to produce large concentrations of negative sample ions under CI conditions. Negative ions are detected by reversing the polarity of the magnet and employing a positive accelerating voltage.^{2-3,5} Negative CI is more sensitive than positive CI when a substituent atom or functional group of high electron affinity is present in the molecule.

An extended application of CI is atmospheric pressure (API) mass spectrometry.⁶ In this method, the ionization process occurs in a reaction chamber external to a quadrupole mass analyzer. The reaction chamber is at atmospheric pressure and ions and neutral molecules enter the low pressure region through a small aperture in a metal disc which forms one wall of the reaction chamber.

Gas chromatographic effluents are ideally suited as input to CI sources provided: (1) the carrier gas and reagent gas are one and the same, (2) the pressure drop between the outlet of the GC column and the ion source is relatively small, and (3) the sample is small, in which case GC-MS offers the most efficient method of sample introduction.

CI mass spectrometry has been employed to study derivatives of isomeric 2,3-dimethyl-1,4-cyclopentanediols, where it was found that the degree of loss of groups was strongly dependent on the stereochemistry of the molecule permitting differentiation between isomers,⁷ and also to study the mechanism of olefin elimination in alkyl-substituted benzenes, where it was found that hydrogen migrations occur not by scrambling but by competition involving cyclic transition states of different ring sizes.⁸ Other studies have included a study of alkyl substituted cyclopropanes using methane as reagent gas, which indicated that the reaction can go either by proton addition or hydride abstraction,⁹ and a study of norbornyl derivatives, where it was observed that there is no significant σ -participation in the transition leading to the formation of norbornyl cations.¹⁰

Application of GC-CIMS, especially in the negative mode, has provided some measure of success over other techniques in biomedical,^{3,11} forensic,¹² and environmental studies.^{3,6,13}

Although not as extensively studied as those of organic compounds, the CI mass spectra of a number of organometallic and coordination compounds have also been investigated.¹⁴

The success of the CI technique is due in no small measure to improvements in instrumentation.^{3,15}

BIBLIOGRAPHY

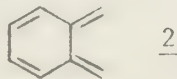
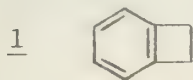
1. M. S. B. Munson and F. H. Field, *J. Am. Chem. Soc.*, 88, 2621 (1966).
2. "Mass Spectrometry", Vol. 4, R. A. W. Johnstone, Sr., reporter, Specialist Periodical Reports, The Chemical Society, London, 1977.
3. A. L. Burlingame, C. H. L. Shackleton, I. Howe, and O. S. Chizhov, *Anal. Chem.*, 50, 346R (1978).
4. W. J. Richter and H. Schwarz, *Angew. Chem. Int. Ed. Engl.*, 17, 424 (1978).
5. D. F. Hunt and S. K. Sethi, in "High Performance Mass Spectrometry: Chemical Applications", M. L. Gross, ed., ACS Symposium Series, no. 70, 1978, p. 150.
6. E. C. Horning, D. I. Carroll, I. Dzidic, S.-N. Lin, R. N. Stillwell, and J.-P. Thenot, *J. Chromatogr.*, 142, 481 (1977).
7. M. Claeys and D. Van Hauer, *Org. Mass Spectrom.*, 12, 531 (1977).
8. H.-W. Leung and A. G. Harrison, *Org. Mass. Spectrom.*, 12, 582 (1977).
9. A. H. Audrist, P. J. Gemperline, and H.-C. Chen, *Org. Mass Spectrom.*, 13, 272 (1978).
10. B. L. Jelus, D. L. Dalrymple, J. Michnowicz, and B. Munson, *Org. Mass Spectrom.*, 13, 163 (1978).
11. (a) A. Blum, M. D. Gold, B. N. Ames, C. Kenyon, F. R. Jones, E. A. Hett, R. C. Dougherty, E. C. Horning, I. Dzidic, D. I. Carroll, R. N. Stillwell, and J.-P. Thenot, *Science*, 201, 1020 (1978); (b) A. J. Lewy and S. P. Markey, *ibid.*, 201, 241 (1978); (c) R. J. W. Truscott, D. G. Burke, J. Korth, B. Halpern, and R. Summons, *Biomed. Mass Spectrom.*, 5, 477 (1978).
12. J. M. Chao, R. Saferstein, and J. Manura, *Anal. Chem.*, 46, 296 (1974).
13. (a) J. R. Hass, M. D. Friesen, D. J. Harvan, and E. C. Parker, *Anal. Chem.*, 50, 1474 (1978); (b) R. C. Dougherty and K. Piotrowska, *Proc. Natl. Acad. Sci. U.S.A.*, 73, 1777 (1976).
14. (a) J. H. Bowie and B. D. Williams in "Mass Spectrometry", A. Maccoll, ed., M.T.P. International Review of Science, Series Two, Vol. 5, Butterworth, London, 1975, p. 89; (b) M. R. Blake, J. L. Garnett, I. K. Gregor, and S. B. Wild, *Org. Mass Spectrom.*, 13, 20 (1978); (c) E. R. Prescott, J. E. Campana, and T. H. Risby, *Anal. Chem.*, 49, 1501 (1977); (d) S. D. Goff, B. L. Jelus, and E. E. Schweizer, *Org. Mass Spectrom.*, 12, 33 (1977); (e) D. R. Dakternieks, I. W. Frazer, J. L. Garnett, and I. K. Gregor, *Org. Mass Spectrom.*, 12, 370 (1977).
15. (a) S. C. S. Rao and C. Fenselau, *Anal. Chem.*, 50, 511 (1978); (b) R. D. Smith and P. W. Ryan, *Anal. Chem.*, 50, 371 (1978).

BENZOCYCLOBUTENES: A QUINODIMETHANE EQUIVALENT

Reported by Kenneth Moder

February 5, 1979

Benzocyclobutenes, like the parent molecule (1), have become important, reliable, and convenient sources of quinodimethanes (2). The versatility of benzocyclobutenes lies in their accessibility and chemical inertness. These properties allow chemical modification and substitution of both the aromatic and the four-member rings.¹ This seminar will discuss the synthetic uses of benzocyclobutenes; however, benzocyclobutendiones² will not be discussed.



Numerous approaches to o-quinodimethanes are known such as thermal and photochemical chelotropic eliminations of sulfur dioxide, nitrogen, and others.³ These routes, however, do not present the same versatility as benzocyclobutenes. Benzocyclobutenes are readily available by base-induced cyclization of o-halodihydrocinnamionitriles,⁴ cycloaddition of benzyne with olefins,⁵ halogen/lithium exchange of 2-(2-halophenyl) ethyl bromides,⁶ thermal decomposition of isochromanones,⁷ or by cobalt-catalyzed cooligomerization.⁸

Benzocyclobutenes have been shown to undergo efficient Diels-Alder reactions with olefinic and acetylenic dienophiles,³ as well as carbonyl, imino, and nitrile dienophiles.⁹ The ease of retrocycloaddition for benzocyclobutenes can be altered by substitution on the four-member ring. The stabilities of some monosubstituted derivatives are reflected in the approximate temperature for retrocycloaddition (3-4) and Table 1.³ Substitution on the four-membered ring also affects the stereochemistry of the ring opening.¹⁰

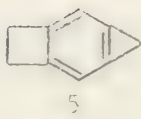


Table 1

Substituent, R:	NH ₂	OH	NHCOR'	C=O	CH ₂	H
Temperature, °C:	25	80	110	150	180	200

A crucial test of the synthetic utility of benzocyclobutenes has only recently been demonstrated in the synthesis of natural products. Benzocyclobutenes have been used to construct isoquinoline alkaloids, such as protoberberine, spirobenzyl isoquinoline, olivancine, yohimbine, and some diterpene alkaloids.¹¹ Benzocyclobutenes have also been effectively utilized in the synthesis of steroids like estrone,¹² di-^{13a} and tri-terpenes^{13b} like hibaene and alnusenone, tetracyclines like adriamycinone,^{11d} and for some polycycles.¹⁴

Benzocyclobutenes have also been employed in the synthesis of highly strained molecules of theoretical interest (5)¹⁵ and of cyclobutenbenzyne.¹⁶



Some recent work by Riemann may open new areas of o-quinodimethane chemistry with the synthesis of cyclobutapyridines.¹⁷

It is evident that benzocyclobutenes will, in the future, contribute even more in their role as stable quinodimethane equivalents.

BIBLIOGRAPHY

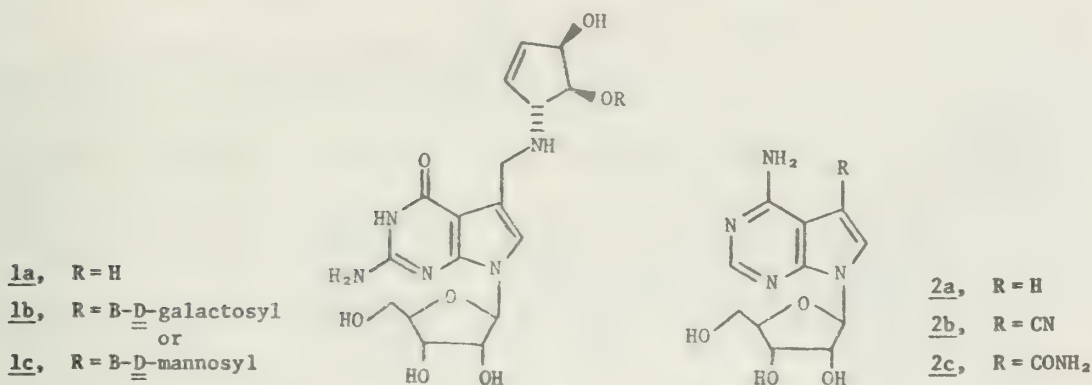
1. (a) I. L. Klundt, *Chem. Rev.*, 70, 471 (1970); (b) W. A. Bubb and S. Sternhell, *Aust. J. Chem.*, 29, 1685 (1976).
2. A. H. Schmidt and W. Reid, *Synthesis*, 1 (1978).
3. W. Oppolzer, *Synthesis*, 793 (1978).
4. (a) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, 27, 3836 (1962); (b) J. A. Skorcz and F. E. Kaminski, *Org. Synth. Coll. Vol.* 5, 263 (1973).
5. H. H. Wassermann and J. Solodar, *J. Am. Chem. Soc.*, 87, 4002 (1965).
6. (a) W. E. Parham, L. D. Jones, and Y. A. Sayed, *J. Org. Chem.*, 41, 1184 (1976); (b) P. D. Brewer, J. Tagat, C. A. Hergrueter, and P. Helquist, *Tetrahedron Lett.*, 4573 (1977).
7. R. J. Spangler, B. G. Beckmann, and J. H. Kim, *J. Org. Chem.*, 42, 2989 (1977).
8. (a) R. L. Hillard, III, and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 99, 4058 (1977); K. P. C. Vollhardt, *Acc. Chem. Res.*, 10, 1 (1977).
9. W. Oppolzer, *Angew. Chem. Int. Ed.*, 16, 10 (1977).
10. T. Kametani, M. Tsubuki, Y. Shiratori, Y. Koto, H. Nemoto, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 42, 2672 (1977).
11. (a) Y. Kondo, *Heterocycles*, 4, 197 (1976); (b) T. Kametani and K. Fukumoto, *Acc. Chem. Res.*, 9, 319 (1976); (c) T. Kametani and K. Fukumoto, *Heterocycles*, 7, 615 (1977); (d) T. Kametani, *ibid.*, 8, 465 (1977); (e) T. Kametani, Y. Kato, F. Satoh, and K. Fukumoto, *J. Org. Chem.*, 42, 1177 (1977).
12. (a) T. Kametani, H. Nemoto, H. Ishikawa, and K. Shiroyama, *J. Am. Chem. Soc.*, 98, 3378 (1976); (b) R. L. Funk and K. P. C. Vollhardt, *ibid.*, 99, 5483 (1977); (c) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, H. Matsumoto, and K. Fukumoto, *ibid.*, 99, 3461 (1977); (d) W. Oppolzer, M. Petrzilka, and K. Bättig, *Helv. Chim. Acta*, 60, 2964 (1977); (e) T. Kametani, H. Matsumoto, H. Nemoto, and K. Fukumoto, *J. Am. Chem. Soc.*, 100, 6218 (1978); (f) R. L. Funk and K. P. C. Vollhardt, *ibid.*, 101, 215 (1979).
13. (a) T. Kametani, Y. Kato, J. Hondo, and K. Fukumoto, *ibid.*, 98, 8185 (1976); (b) T. Kametani, Y. Hirai, Y. Shiratori, and K. Fukumoto, *ibid.*, 100, 554 (1978).
14. R. L. Funk and K. P. C. Vollhardt, *ibid.*, 98, 6755 (1976).
15. (a) R. D. Miller, J. Kolc, and J. Michl, *ibid.*, 98, 8510 (1976); (b) R. P. Thummel and W. Nutakul, *J. Org. Chem.*, 42, 300 (1977); (c) D. Daralian, P. J. Garratt, and M. M. Mansuri, *J. Am. Chem. Soc.*, 100, 980 (1978); (d) R. Gray, L. C. Harruff, J. Krymowski, J. Peterson, and V. Boekelheide, *ibid.*, 100, 2892 (1978); (e) H. Hart, M. Jeffares, A. Teuerstein, and D. L. Ward, *ibid.*, 100, 8012 (1978).
16. (a) R. L. Hillard, III, and K. P. C. Vollhardt, *ibid.*, 98, 3579 (1976); (b) R. L. Hillard, III, and K. P. C. Vollhardt, *Angew. Chem. Int. Ed.*, 16, 399 (1977).
17. R. P. Thummel and D. K. Koli, *J. Org. Chem.*, 43, 4882 (1978).

NUCLEOSIDE Q

Reported by Joseph B. Holtwick

February 8, 1979

The recently isolated nucleosides Q (1a) and Q* (1b and 1c), the only ribonucleic acid (RNA) isolated nucleosides which are skeletally modified, as well as the nucleoside antibiotics tubercidin (2a), toyocamycin (2b) and sangivamycin (2c), are all exocyclic substitutional variants of the pyrrolo[2,3-d]pyrimidine ring system. Elucidation of the structures of tubercidin,¹⁻⁴ toyocamycin⁵⁻⁹ and sangivamycin¹⁰ coupled with their broad spectrum of chemotherapeutic and biological activity¹¹ has prompted synthetic preparation of pyrrolo[2,3-d]pyrimidines, including the nucleoside antibiotics 2 and related derivatives.



Nucleosides Q and Q*, biosynthetically derived from a guanylate residue,¹²⁻¹⁶ have been detected in the tRNAs of a wide variety of organisms, thus suggesting a role in cell growth regulation.¹⁷⁻²²

The synthesis of nucleoside Q requires the resolution of three basic problems: construction of an appropriately functionalized pyrrolo[2,3-d]pyrimidine ring, introduction of the 3β-amino-cyclopent-1-ene-4α,5α-diol and ribosidation. Research efforts have centered on the first of these problems in conjunction with preparation of the nucleoside antibiotics 2.

The preparation of pyrrolo[2,3-d]pyrimidines has been accomplished by four principal methods: (a) from 4-pyrimidinylhydrazones by acid catalyzed or thermally induced reactions analogous to the Fischer indole synthesis,²³⁻²⁵ (b) from appropriately substituted pyrroles followed by pyrimidine ring closure,^{9,25-27} (c) by synthesis of a 4-aminopyrimidine with a potential acetaldehyde (or acetone) group at the C-5 position followed by acid catalyzed cyclization,^{4,28-33} and (d) by closure of 6-aminouracils, 2-amino-6-alkylamino-4-hydroxypyrimidines and related compounds with chloroacetaldehyde or α-halo carbonyl compounds.^{28,34-36}

To date, the synthetic approaches to nucleoside Q have centered upon modification of tubercidin and toyocamycin^{37,38} and approaches of the type (c). This latter approach has resulted in the first total synthesis of nucleoside Q.³³ The material obtained may have contained its side-chain epimer, but neither high-pressure liquid chromatography nor 270 MHz nuclear magnetic resonance spectrum of the acetonide ribosyl aglycone has revealed any evidence of heterogeneity.

BIBLIOGRAPHY

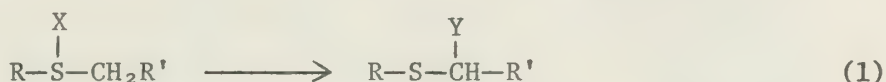
1. S. Suzuki and S. Marumo, *J. Antibiotics* (Tokyo), 13A, 360 (1960).
2. S. Suzuki and S. Marumo, *ibid.*, 14A, 34 (1960).
3. Y. Mizuno, M. Ikehara, K. A. Watanabe, S. Suzaki, and T. Itoh, *J. Org. Chem.*, 28, 3329 (1963).
4. Y. Mizuno, M. Ikehara, K. A. Watanabe, and S. Suzaki, *ibid.*, 28, 3331 (1963).
5. K. Ohkuma, *J. Antibiotics* (Tokyo), 13A, 361 (1960).
6. K. Ohkuma, *ibid.*, 14A, 343 (1961).
7. R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.*, 90, 524 (1968).
8. E. C. Taylor and R. W. Hendess, *ibid.*, 86, 951 (1964).
9. E. C. Taylor and R. W. Hendess, *ibid.*, 87, 1995 (1965).
10. K. V. Rao, *J. Med. Chem.*, 11, 939 (1968).
11. R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, and references therein.
12. H. M. Goodman, J. N. Abelson, A. Landy, S. Zadrazil, and J. D. Smith, *Eur. J. Biochem.*, 13, 461 (1970).
13. C. E. Singer and G. R. Smith, *J. Biol. Chem.*, 247, 2989 (1972).
14. H. J. J. Nijkamp and R. G. De Haan, *Biochem. Biophys. Acta*, 145, 31 (1967).
15. Y. Kuchino, H. Kasai, K. Nihei, and S. Nishimura, *Nucleic Acids Res.*, 3, 393 (1976).
16. R. J. Suhadolnik and T. Uematsu, *J. Biol. Chem.*, 245, 4365 (1970).
17. H. M. Goodman, J. Abelson, A. Landy, S. Bunner, and J. D. Smith, *Nature* (London), 217, 1019 (1968).
18. U. L. RajBhandary, S. H. Chang, H. J. Gross, F. Harada, F. Kimura, and S. Nishimura, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 28, 409 (1969).
19. B. P. Doctor, J. E. Loebel, M. A. Sodd, and D. B. Winter, *Science*, 163, 693 (1968).
20. F. Harada and S. Nishimura, *Biochemistry*, 11, 301 (1972).
21. B. N. White, G. M. Tener, J. Holden, and D. T. Suzuki, *J. Mol. Biol.*, 74, 635 (1973).
22. H. Kasai, Y. Kuchino, K. Nihei, and S. Nishimura, *Nucleic Acids Res.*, 2, 1931 (1975).
23. P. A. Crooks and B. Robinson, *Chem. Ind. (London)*, 547 (1967).
24. S. Senda and K. Hirota, *Chem. Letters*, 367 (1972).
25. T. D. Duffy and D. G. Wibberley, *J. Chem. Soc., Perkin Trans. 1*, 1921 (1974).
26. H. Wamhoff and B. Wehling, *Chem. Ber.*, 109, 2983 (1976).
27. R. L. Tolman, R. K. Robbins, and L. B. Townsend, *J. Am. Chem. Soc.*, 91, 2102 (1969).
28. Wellcome Foundation, British Patent 812 366 (1959); *Chem. Abstr.*, 54, 5921 (1960).
29. J. Davoll, *J. Chem. Soc.*, 131 (1960).
30. E. Bisagin, J. P. Marquet, and J. Andre-Louisfert, *Bull. Soc. Chim. Fr.*, 803 (1969).
31. F. Seela and U. Lupke, *Chem. Ber.*, 110, 1462 (1977).
32. T. Kondo, T. Ohgi, and T. Goto, *Agric. Biol. Chem.*, 41, 1501 (1977).
33. T. Ohgi, T. Goto, H. Kasai, and S. Nishimura, *Tetrahedron Lett.*, 367 (1976).
34. J. A. Secrist, III, and P. S. Liu, *J. Org. Chem.*, 43, 3937 (1978).
35. C. W. Noell and R. K. Robins, *J. Heterocycl. Chem.*, 1, 34 (1964).
36. E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, 30, 655 (1965).
37. C. S. Cheng, B. C. Hinshaw, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.*, 98, 7870 (1976).
38. L. B. Townsend, R. L. Tolman, R. K. Robins, and G. H. Milne, *J. Heterocycl. Chem.*, 13, 1363 (1976).

PUMMERER REARRANGEMENTS

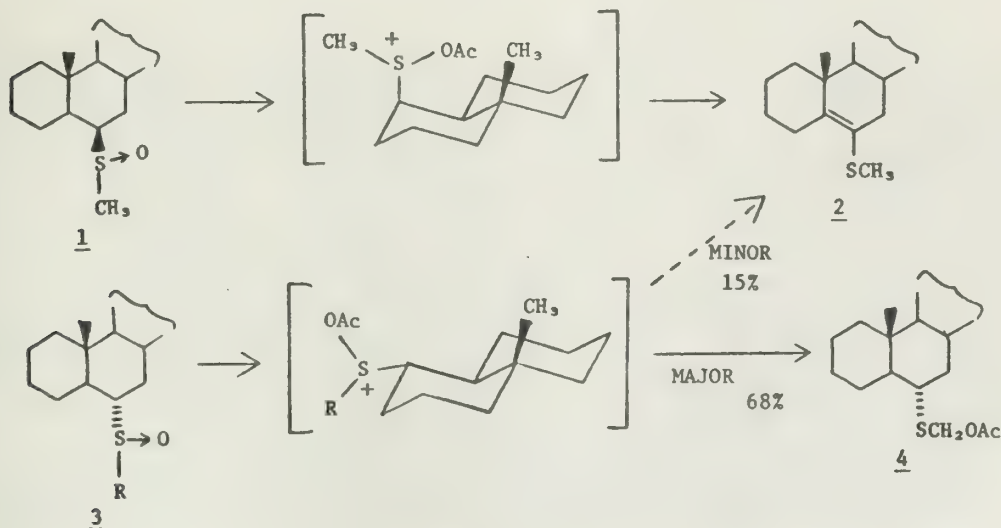
Reported by John M. Finn

February 19, 1979

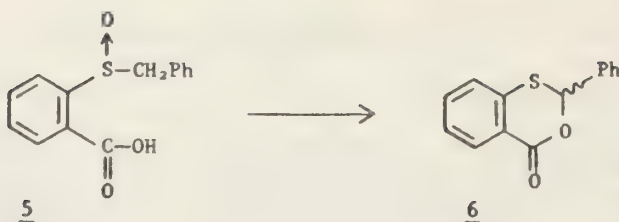
The name Pummerer reaction has been used to describe the class of reactions in which a sulfonium sulfur is reduced with concomitant oxidation of the α -carbon atom (Eq. 1).¹ The reaction of sulfoxides with acetic anhydride leading to α -acetoxy sulfides has been known since 1910.² This reaction may also be initiated by various mineral acids, acid halides, D.C.C., isocyanates, ketenes, and inorganic halides. Durst has reviewed these rearrangements prior to 1969.³ This report will emphasize more recent applications.



Pummerer rearrangements usually proceed with high regioselectivity, substitution occurring at the more acidic α -carbon atom.⁴ For dialkyl sulfoxides the order of reactivity is $\text{CH}_3 > \text{CH}_2\text{R} > \text{CHR}_2$. An exception to this regioselectivity was observed by Jones for steroidal sulfoxides.⁵ When the 6β -sulfoxide 1 was allowed to react with acetic anhydride in refluxing benzene, 2 was produced. Similar treatment of the 6α -sulfoxide 3 gave 4, the expected isomer, as the major product and 2 as a minor component. This selectivity is explained by considering the relief of steric strain produced by proton abstraction from the steroid skeleton in 1.



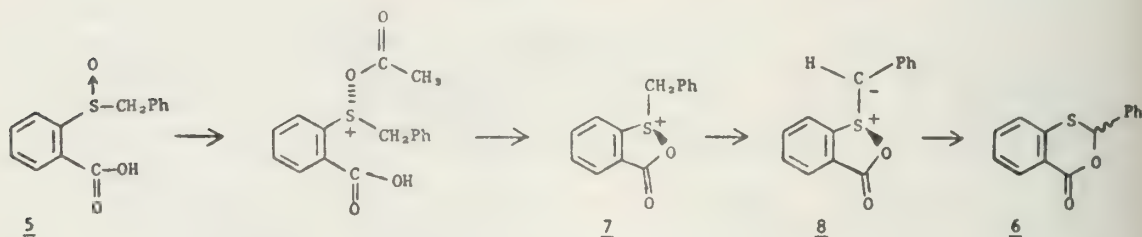
Asymmetric Induction. Pummerer rearrangements of sulfoxides to α -acetoxy sulfides are of interest stereochemically since the chirality at sulfur may be transferred to the α -carbon atom. Allenmark was the first to observe asymmetric induction in a Pummerer rearrangement.⁶ When allowed to react with DCC in 1,2-dichloroethane, optically active 5 produced the cyclic optically active product 6 in 30% enantiomeric excess. In different solvents with either DCC or acetic anhydride, 6 was produced in varying amounts of enantiomeric enrichment. However, when *p*-toluenesulfonic acid was used, the product 6 was racemic.



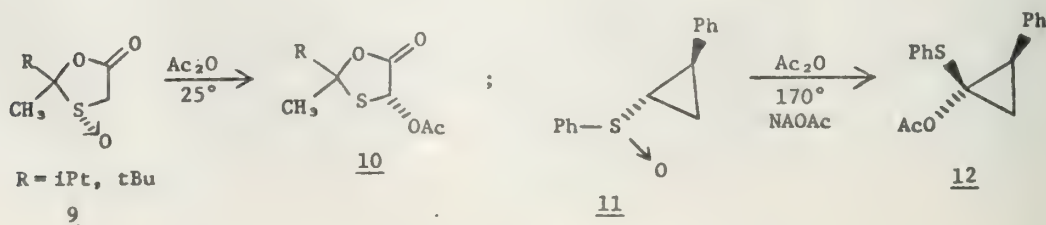
Kinetic studies of the reaction of **5** with acetic anhydride have shown this reaction to be quite different from most Pummerer rearrangements.⁷ When compared to *p*-carboxyphenyl benzyl sulfoxide the reaction of **5** is over 130 times faster. An isotope effect of (1.08) is much smaller than (2.85)⁸ reported for other Pummerer reactions. When the benzyl group is replaced by various alkyl groups, the expected order of reactivity is reversed; that is, *i*-Pr > *n*-Pr > CH₃ > CH₂Ph. These results suggest that the initial acylation is the rate-determination step.

Similar mechanisms for the reaction of **5** to **6** have been proposed by Oae and Allenmark^{6,7} (Scheme I). Intramolecular attack of the oxysulfonium ion by the *ortho* carboxyl group forms a five-membered cyclic intermediate **7**. Differential proton abstraction of diastereotropic protons produces an ylide **8**. Subsequent 1,2-shift of the acetoxy group affords a chiral product **6**. It has been suggested that the failure of *p*-toluene sulfonic acid to produce any asymmetric induction is due to a change in mechanism in which an achiral carbonium ion is formed.

Scheme I



There is precedent for very stereoselective Pummerer reactions. When allowed to react with acetic anhydride, 2,2-dialkyl-1,3-oxathiolan-5-one-S-oxides **9** were converted to 4-acetoxy-2,2-dialkyl-1,3-oxathiolan-5-ones **10** with the acetoxy group introduced predominantly (85-90%) on the same side of the ring as formerly occupied by the S-oxide bond.⁹ More recently, Oae has reported that *trans*-2-phenyl-1-(phenylsulfinyl) cyclopropane **11** when allowed to react with acetic anhydride containing sodium acetate at 170° produces exclusively *cis*-2-thiophenoxy-*trans*-2-acetoxy-1-phenylcyclopropane **12**.¹⁰ Other substituted cyclopropanes also react with high (>75%) stereoselectivity. Both of these studies, however, suffer from a lack of rigorous structural assignments.

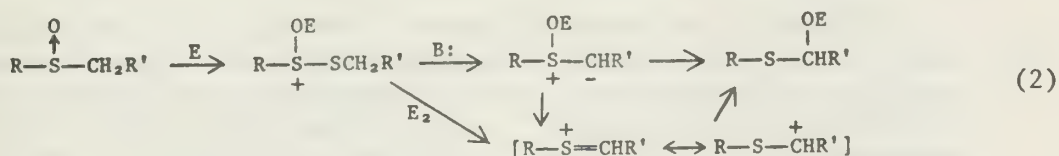


Asymmetric induction has been observed in other Pummerer reactions. These have in common sulfoxides with highly acidic α -protons. The results of asymmetric Pummerer reactions are summarized in Table 1.

Table 1

Sulfoxide	Product	Electrophile/Solvent	Rotation	$\Sigma e e$	Σ yield
		DCC/(CH ₂ Cl) ₂	-46.3°	29.9	91
		DCC/ ϕ H	-19.4°	12.5	31
		DCC, H ₃ PO ₄ /(CH ₃) ₂ CO	+18.0°	11.6	64
		Ac ₂ O/Ac ₂ O	+17.3°	11.2	95
		Ac ₂ O/Ac ₂ O	+26.8°	29.0	90
		Ac ₂ O/Ac ₂ O	+2.2°	—	40
		Ac ₂ O/Ac ₂ O	-4.0°	24.0	73

Studies with optically active substrates are of mechanistic importance. The most often proposed mechanism for Pummerer rearrangements, involving an achiral sulfur-stabilized carbonium ion, must be modified to include intramolecular 1,2-shifts (Eq. 2). The intermediate first formed is an

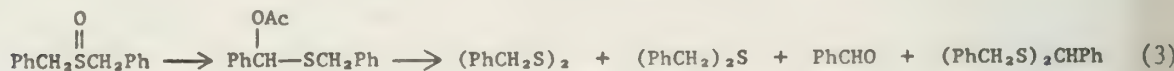


oxysulfonium ion. Methoxysulfonium fluoroborates have been isolated and undergo Pummerer reaction on treatment with base.¹² Proton abstraction by base forming an ylide has been postulated to explain the regioselectivity. Deuterium incorporation in recovered sulfoxide, when the reaction is run in deuterated methanol, supports this claim.¹³ The formation of alkylidene sulfonium ions has been widely suggested.³ A carbonium ion rearrangement observed by Parham¹⁴ and a crossover of labeled oxygens in the Pummerer reaction of methylarylmethoxy-oxysulfonium ions under non-exchanging conditions,¹² have been the main basis for these suggestions. Parham, however, failed to find similar carbonium ion rearrangements in several other cases in which rearrangements might be expected¹⁵ and the generality of the alkylidene sulfonium ions can be questioned. An E₂ elimination of the oxysulfonium ion has been suggested as an alternate pathway not involving an ylide.¹ Intramolecular 1,2-shifts of ylides has been suggested to explain asymmetric induction.¹¹

Although the degrees of asymmetric induction produced thus far are modest, marked improvements might be expected. Oae has studied the racemization of sulfoxides under Pummerer conditions and has found that racemization due to acetoxy exchange is as fast or faster than Pummerer rearrangements in several cases.¹⁵ The rate of this racemization is a factor limiting the degree of asymmetric induction observed. When the reaction of *p*-tolyl-prop-2-ynyl sulfoxide with acetic anhydride is quenched after 40% conversion, the recovered sulfoxide is 91% racemized.^{11c} Similarly, when the reaction of *o*-carboxyphenyl benzyl sulfoxide **5** with acetic anhydride is quenched after 3 minutes, 37% of the starting

sulfoxide is recovered with 38% of the original activity.⁶ Since Pummerer reactions are very sensitive to the conditions employed, it might be expected that careful control of experimental conditions will produce products of high optical activity.

Synthetic Applications. Although the Pummerer reaction is very old and well known, it has been of limited synthetic utility until recently. For simple dialkyl sulfoxides, yields are generally good (85-95%).¹⁶ But for more complicated sulfoxides, yields are substantially reduced and side products are formed. The reaction conditions generally require prolonged reflux at relatively high temperatures in the presence of acid or base; such conditions are not compatible with many organic compounds.¹⁷ When dibenzyl sulfoxide is treated with acetic anhydride, the α -acetoxy sulfide formed is not stable and appreciable amounts of benzyl disulfide, benzyl sulfide, benzaldehyde, and α,α -bisbenzylthiotoluene are formed (Eq. 3).^{1,18} Besides these side products, some α -acetoxy sulfides readily eliminate to give α,β -unsaturated sulfides.^{19,20} Such production of unsaturated sulfides with benzoic anhydride is one of the oldest uses of Pummerer reactions.

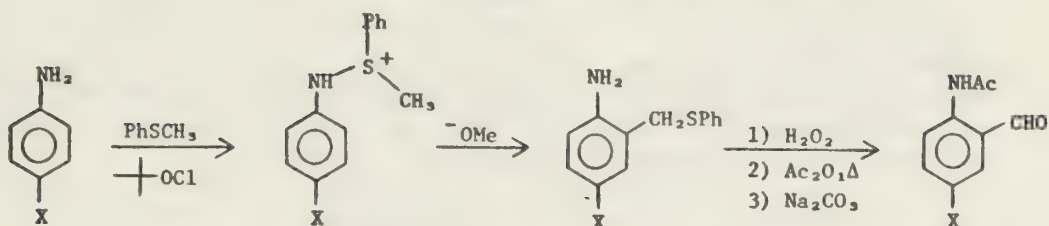


The recent advances in Pummerer reactions are the result of modification of reaction conditions employed. The use of trifluoroacetic and acetic mixed anhydride allows the reaction to take place in mild conditions room temperature or below.²¹ This method gives yields 10-20% higher than previous methods. The advent of preparative liquid chromatography has also greatly expanded the use of Pummerer reactions since mixtures of products which were previously difficult to separate are often encountered.

The α -acetoxy sulfides formed from a Pummerer reaction may be considered latent aldehydes. Tsuchihashi has found that use of buffers such as pyridine or sodium acetate in the solution protects the product from decomposition.²² The starting sulfoxides are easily obtained by the reaction of alkyl halides with *p*-tolylsulfenyl carbanion or by oxidation of the alkyl *p*-toluene sulfide produced from the reaction of an alkyl halide with sodium *p*-toluenethiolate. Both of these routes produce sulfoxides typically in 80-95% yields. Basic hydrolysis of α -acetoxy sulfides produces aldehydes in high yield. An example of the use of Pummerer rearrangements to introduce aldehyde functionality is Kendo's synthesis of a prostaglandin intermediate.²³

A method of selective ortho formylation of aromatic amines is produced when a Pummerer reaction is coupled to the introduction of a phenylthiomethyl group to an aniline. When a chlorosulfonium salt is allowed to react with an aromatic amine followed by treatment with sodium methoxide, a phenylthiomethyl group is introduced in the ortho position.²⁴ Oxidation to sulfoxide, Pummerer rearrangement, and basic hydrolysis affords the aldehyde in relatively high overall yield (Scheme II). Since the addition of methylthiomethyl groups to phenols has been described,²⁵ this method is probably applicable to phenolic systems as well.

Scheme II



The aldehyde synthesis is very general and can be expanded to β -hydroxy sulfoxides, which when treated with acetic anhydride-sodium acetate at reflux for 3 hours produces the corresponding 1,2-diacetoxy sulfides (Eq. 4).²⁶ Yields are generally high (Table 2).

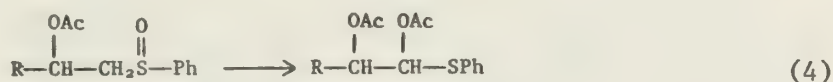
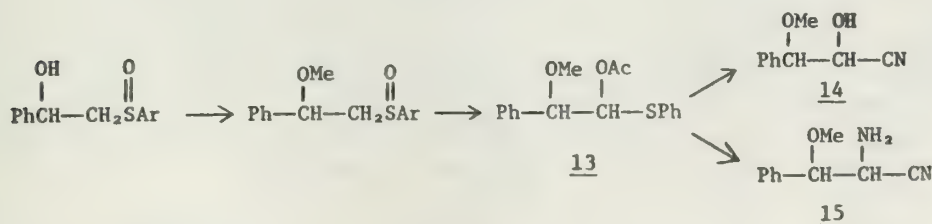


Table 2

R	Yield%
CH ₃ -	90
CH ₃ CH ₂ CH ₂ -	71
AcOCH ₂ -	90
PhCH ₂ -	74
Ph-	95

β -Hydroxy sulfoxides are readily obtained by the addition of phenylsulfinyl carbanion to aldehydes. With the β -hydroxy function protected as a methyl ether, the product of a Pummerer reaction, a 2-methoxy-1-acetoxy sulfide 13, is a versatile intermediate. Reaction with sodium cyanide produces a 1-methoxy-2-hydroxy nitrile 14. Treatment of 13 with sodium cyanide followed by ammonium chloride affords the α -amino nitrile 15. In these reactions, displacement of thiophenoxide occurs exclusively.

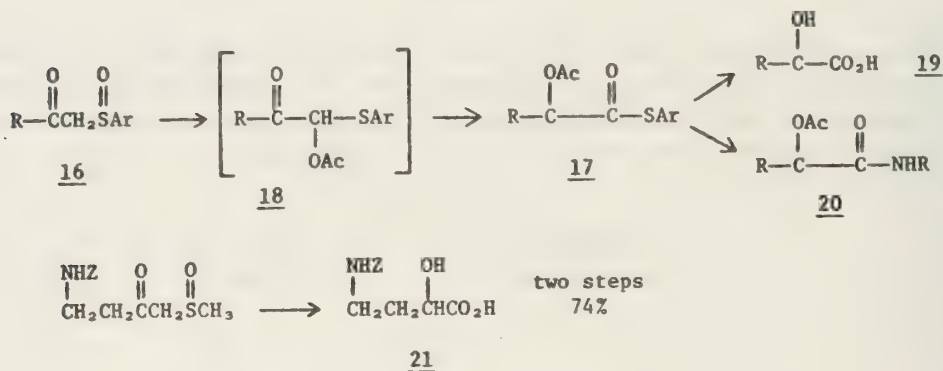
Scheme III



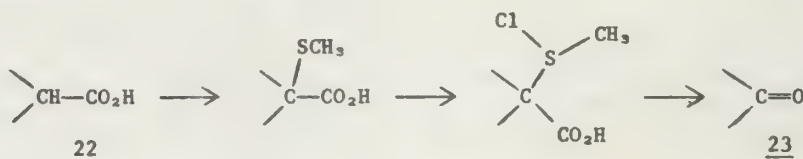
Potential for asymmetric synthesis exists. The reactions of α -methylsulfinyl anions with aldehydes are very stereoselective.²⁷ The Pummerer reaction may be highly stereoselective, as described earlier, and since both the α -acetoxy sulfide 13 and the α -acetoxy nitrile 14 are produced in 6:4 diastereomeric mixtures, there is reason to believe the substitution reaction is stereoselective.

Treatment of β -keto sulfoxides 16 in the presence of base affords unexpected α -acetoxy acid thioesters 17 in high yields (80-90%).²⁸ The expected product 18²⁹ is formed in neutral conditions but is rapidly converted to 17 by base. The ester 17 can be hydrolyzed with sodium hydroxide to α -hydroxy acids 19. Reactions of 17 with various amines produces amides 20. This reaction has been applied to the synthesis of an antibiotic 4-amino-2-hydroxybutyric acid 21.

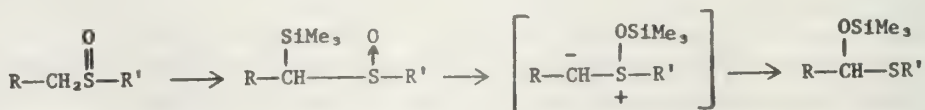
Scheme IV



Pummerer reactions have been utilized in other ways. McElhinney used the reaction to introduce acetoxy groups in thio-sugars with some stereochemical control.³⁰ Similarly, functionality at the C-2 position of cephalosporins can be introduced.³¹ DeWaard has developed a [1,4] inversion of functionalized isoprenes utilizing a Pummerer reaction.³² Trost has developed a means of oxidative decarboxylation.³³ A dianion of a carboxylic acid 22 is sulfenylated. Reaction of the α -thiomethyl carboxylic acid with N-chlorosuccinimide produces a carbonyl compound 23 after acid hydrolysis.

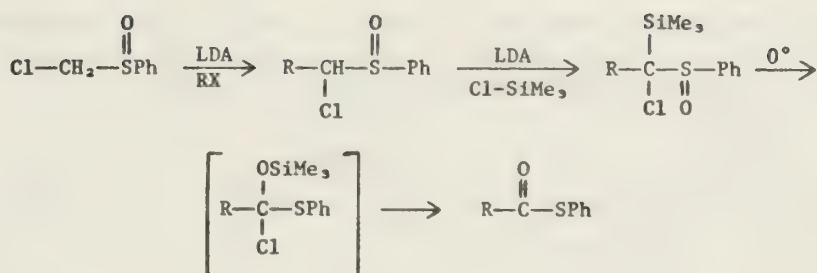


α -Trimethylsilyl sulfoxides were found to undergo a facile rearrangement to α -trimethylsiloxy sulfides under mild conditions.³⁴ This silicon-Pummerer reaction is observed below room temperature when dialkyl sulfoxides are used.³⁵ The rearranged products are obtained by silylation of the sulfoxide at -78° followed by warming to room temperature. Although the yields are modest (~45%), the transformations shown are not observed, in many cases, under typical Pummerer conditions.



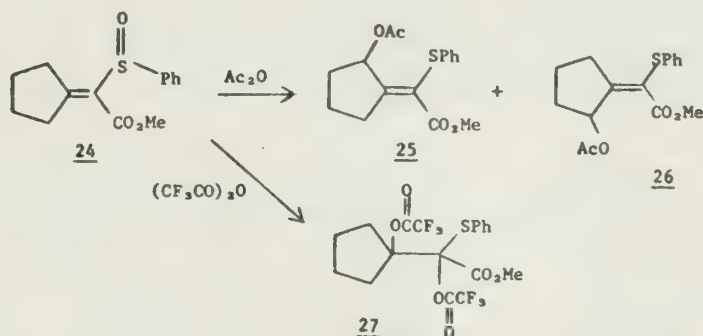
Applying this silicon-Pummerer reaction to α -chloro sulfoxides produces thioesters in moderately high yields (60 - 70%) at 0°C .³⁶ In this reaction, the starting sulfoxide may be considered a thioester acyl anion equivalent.

Scheme V



It was initially felt that vinyl sulfoxides were unreactive under Pummerer conditions.^{4b} While this may be true for some simple vinyl sulfoxides, several interesting reactions of more complex vinyl sulfoxides have been reported. Methyl cyclopentylidene (phenylsulfinyl) acetate 24 on treatment with acetic anhydride affords two regioisomers 25 and 26 produced by a vinylogous Pummerer reaction.³⁷ When 24 is treated with more reactive trifluoroacetic anhydride the product of an "additive Pummerer reaction", 27, is formed.³⁸ Additive Pummerer reactions have also been reported by O'Sullivan and King.³⁹ Such reactions are potentially useful since they introduce several functionalities at once.

Scheme VI



Pummerer rearrangements are useful in the synthesis of cyclic compounds. The intramolecular nature of these reactions allow milder conditions to be employed. With a nucleophilic aromatic system suitably arranged, various cyclic systems may be formed. For example, 3,4-dimethoxyphenethyl methylsulfinyl methyl ketone 28, when treated with trifluoroacetic anhydride, undergoes cyclization to form 29 in 70% yield.⁴⁰ Similar reactions can be carried out with indole systems.

Table 3

Reactant	Product	Yield
<p><u>28</u></p>	<p><u>29</u></p>	70%
		<p>R = H R' = H 46%</p> <p>R = CH₃ R' = H 60%</p> <p>R = CH₃ R' = NHCOCH₃ 41%</p>

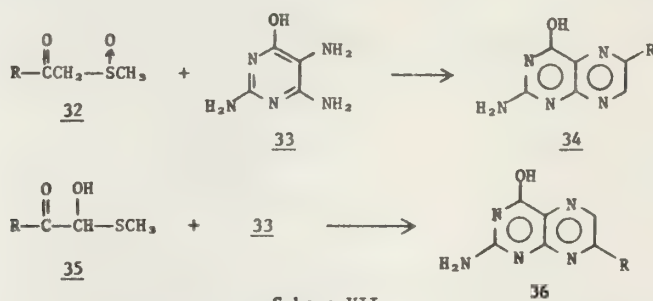
This method has been applied to the synthesis of carbazoles.⁴¹ The syntheses of olivacine and ellipticine have been described.

With suitably arranged alcohols, amides, and acids, intramolecular Pummerer reactions will give rise to heterocyclic compounds.⁴² These reactions usually proceed in high yield (Table 4).

Table 4

Reactant	Product	Yield
		95%
		67%

This route can be applied to the synthesis of pteridines.⁴³ When a β -ketosulfoxide 32 is allowed to react with 2,4,5-triamino-6-hydroxyprimidine 33, the 6-substituted pteridine 34 was formed with no contamination of the 7-isomer 36. It was found that the 7-isomer 36 could be formed exclusively when the hemithioacetal 35, obtained from a Pummerer reaction, was allowed to react with 33. This method constitutes one of the most convenient syntheses of these natural products.



Scheme VII

BIBLIOGRAPHY

1. G. Wilson and C. Strong, *J. Org. Chem.*, 37, 2376 (1972).
2. R. Pummerer, *Chem. Ber.*, 43, 1401 (1910).
3. T. Durst, "Advances in Organic Chemistry", Vol. 6, E. C. Taylor and H. Wymberg, eds., Interscience, New York, 1966, pp. 356-365.
4. (a) C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Lett.*, 5299 (1967); (b) W. E. Parham and L. D. Edwards, *J. Org. Chem.*, 33, 4150 (1968).
5. D. N. Jones, E. Helmy, and R. D. Whitehouse, *J. Chem. Soc., Perkin I*, 1329 (1972).
6. (a) B. Stridsberg and S. Allenmark, *Acta Chem. Scand., Ser. B*, 28, 591 (1974); (b) B. Stridsberg and S. Allenmark, *ibid.*, 30, 219 (1976).
7. T. Numata and S. Oae, *Tetrahedron*, 32, 2699 (1976).
8. S. Oae and M. Kise, *Tetrahedron Lett.*, 2261 (1968).
9. S. Glue, I. T. Kay, and M. R. Kipps, *Chem. Commun.*, 1158 (1970).

10. T. Masuda, T. Numata, N. Furukawa, and S. Oae, *Chem. Lett.*, 903 (1977).
11. (a) M. Mikolajczyk, A. Zatorski, S. Grzejszak, B. Costisella, and W. Midura, *J. Org. Chem.*, 43, 2518 (1978); (b) T. Numata and S. Oae, *Tetrahedron Lett.*, 1337 (1977); (c) T. Numata, O. Itoh, and S. Oae, *Chem. Lett.*, 909 (1977).
12. C. R. Johnson and W. G. Phillips, *J. Am. Chem. Soc.*, 91, 682 (1969).
13. C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, 32, 1926 (1967).
14. W. E. Parham and M. P. Bhavsar, *J. Org. Chem.*, 28, 2686 (1963).
15. (a) S. Oae and M. Kise, *Tetrahedron Lett.*, 1409 (1967); (b) S. Oae and M. Kise, *Bull. Chem. Soc. Jap.*, 43, 1416 (1970); (c) M. Kise and S. Oae, *ibid.*, 43, 1421 (1970); (d) M. Kise and S. Oae, *ibid.*, 43, 1426 (1970).
16. L. Horner and P. Kaiser, *Justus Liebigs, Ann. Chem.*, 626, 19 (1959).
17. B. Trost and T. N. Salzman, *J. Am. Chem. Soc.*, 95, 6840 (1973).
18. D. A. Davenport, D. B. Moss, J. E. Rhodes, and J. A. Walsh, *J. Org. Chem.*, 34, 3353 (1969).
19. W. E. Parham, L. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, 29, 2211 (1964).
20. W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, 83, 4039 (1961).
21. R. Tanikaga, Y. Yabuki, N. Ono, and A. Kaji, *Tetrahedron Lett.*, 2257 (1976).
22. S. Iriuchijima, T. Sakakihara, and G. Tsuchihashi, *Agr. Biol. Chem.*, 40, 1369 (1976).
23. K. Kondo, E. Hiro, and D. Tunemoto, *Tetrahedron Lett.*, 4489 (1976).
24. P. Gassman and H. R. Drewes, *J. Am. Chem. Soc.*, 96, 3002 (1974).
25. (a) J. P. Marino, K. E. Pfitzner, and R. A. Olofson, *Tetrahedron*, 27, 4181 (1971); (b) R. A. Olofson, and J. P. Marino, *ibid.*, 27, 3195 (1971).
26. (a) S. Iriuchijima, K. Maniwa, and G. Tsuchihashi, *J. Am. Chem. Soc.*, 96, 4280 (1974); (b) S. Iriuchijima, K. Maniwa, and G. Tsuchihashi, *Agr. Biol. Chem.*, 40, 2389 (1976).
27. G. Tsuchihashi, S. Iriuchijima, and M. Ishibashi, *Tetrahedron Lett.*, 4605 (1972).
28. S. Iriuchijima, K. Maniwa, and G. Tsuchihashi, *J. Am. Chem. Soc.*, 97, 596 (1975).
29. (a) G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.*, 88, 5498 (1966); (b) G. A. Russell and E. T. Sabourin, *J. Org. Chem.*, 34, 2336 (1969).
30. J. E. McCormick and R. S. McElhinney, *J. Chem. Soc., Perkin I*, 2533 (1976).
31. D. H. Bremner and M. M. Campbell, *Chem. Commun.*, 538 (1976).
32. P. U. Nederlof, M. J. Moolenaar, E. R. deWaard, and H. O. Huisman, *Tetrahedron*, 34, 2205 (1978).
33. B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, 97, 3528 (1975).
34. A. G. Brook and D. G. Anderson, *Can. J. Chem.*, 46, 2115 (1968).
35. (a) E. Vedejs and M. Mullins, *Tetrahedron Lett.*, 2017 (1975); (b) F. A. Carey and O. Hernandez, *J. Org. Chem.*, 38, 2670 (1973).
36. K. M. Moore and J. Wemple, *J. Org. Chem.*, 43, 2713 (1978).
37. H. Kosugi, H. Uda, and S. Yamagiwa, *Chem. Commun.*, 192 (1975).
38. H. Kosugi, H. Uda, and S. Yamagiwa, *Chem. Commun.*, 71 (1976).
39. (a) L. S. Reamonn and W. I. O'Sullivan, *Chem. Commun.*, 642 (1976); (b) R. R. King, *J. Org. Chem.*, 43, 1262 (1978).
40. Y. Oikawa and O. Yonemitsu, *Tetrahedron Lett.*, 3393 (1972).
41. Y. Oikawa and O. Yonemitsu, *J. Chem. Soc., Perkin I*, 1749 (1976).
42. (a) S. Oae and T. Numata, *Tetrahedron*, 30, 2641 (1974); (b) D. T. O'Connor and M. vonStrandtmann, *J. Org. Chem.*, 39, 1594 (1974).
43. A. Rosawsky and K. Chen, *J. Org. Chem.*, 38, 2073 (1973).

FIRST EVIDENCE OF FIVE-COORDINATE HYPERVALENT CARBON

Reported by Reg Forbus

March 12, 1979

Nucleophilic substitution at saturated carbon is one of the most widely studied reactions in organic chemistry. However, whether reactions of this type proceed via completely concerted pathways or via short-lived high-energy intermediates remains questionable.

The Doering-Zeiss mechanism of solvolysis¹ first suggested the possibility of a meta-stable intermediate. In this mechanism the entering and leaving group are simultaneously bound to the displacing carbon. Since this mechanistic proposal efforts to obtain evidence for this proposed intermediate have been documented.² Success, however, has been limited primarily to further speculation.

Gas phase studies have been directed at studying the mechanism of the S_N2 reaction. One such study using pulsed ICR technique⁴ supports a double well potential energy surface in which the symmetrically bonded pentacoordinate intermediate is at an energy maximum. Calculations at various computational levels⁵ further qualitatively support this experimental observation.

A mechanism has recently been proposed which suggests the possibility of an S_N2 reaction at saturated carbon occurring with retention of configuration from a reactive pentacoordinate species.^{6,7} Theoretical considerations were presented which proposed that compression of two bonds by incorporation of two ligands of the reactive carbon atom into a small ring and the consequent changes in bonding could cause preferred attack of the incoming nucleophile to occur *syn* to the leaving group. Detailed treatments of this model have been elaborated, one requiring the pentacoordinate species to be an intermediate,⁶ another, a transition state.⁷ However, attempts to obtain evidence to support this proposal experimentally are without confirmable success.

We propose an electronic stabilization mechanism of far-reaching consequence for the stabilization of a pentacoordinate hypervalent carbon atom. Further, we present evidence to substantiate the first molecule bearing a five-coordinate hypervalent carbon atom.

BIBLIOGRAPHY

1. W. von E. Doering and H. H. Zeiss, *J. Am. Chem. Soc.*, **75**, 4733 (1953).
2. (a) R. W. Gray, C. B. Chapleo, T. Vergnani, A. S. Dreiding, M. Liesner, and D. Seebach, *Helv. Chim. Acta*, **59**, 1547 (1976); (b) T. El Gomati, D. Lensir, and I. Ugi, *Angew. Chem. Int. Ed. Eng.*, **14**, 59 (1975); (c) R. Breslow, S. Garratt, L. Kaplan, and D. La Follette, *J. Am. Chem. Soc.*, **90**, 4051, 4056 (1968); (d) R. K. Lustgarten, M. Brookhart, and S. Winstein, *Tetrahedron Lett.*, 141 (1971); (e) R. J. Basalay and J. C. Martin, *J. Am. Chem. Soc.*, **95**, 2565, 2572 (1973); (f) W. J. Work and J. C. Martin, unpublished results.
3. References 10-16 of Footnote 4.
4. J. I. Brauman and W. N. Olmstead, *J. Am. Chem. Soc.*, **99**, 4219 (1977).
5. Reference 9 of Footnote 4.
6. P. D. Gillespie and I. Ugi, *Angew. Chem.*, **83**, 493 (1971).
7. (a) W. D. Stohrer, *Chem. Ber.*, **107**, 1795 (1974); (b) W. D. Stohrer and K. R. Schmeider, *ibid.*, **109**, 285 (1976).

TRANSIENT SULFURANES AS REACTION INTERMEDIATES

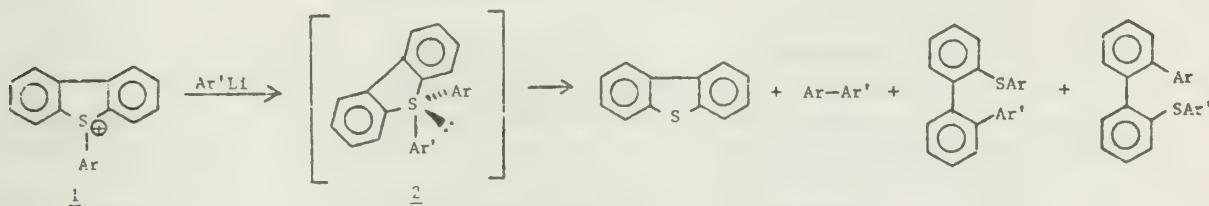
Reported by Thomas A. Sullivan

April 2, 1979

Pentacoordinate, tetravalent organosulfur IV species have been suggested as intermediates in a number of reactions.¹ These species, termed sulfuranes, are hypervalent, having a decet of electrons in the outer shell of sulfur and are considered to be trigonal bipyramidal in their most stable configuration. Compelling evidence for the structure of the sulfuranes and support for their intermediacy in chemical reactions comes from the characterization of stable sulfuranes by Martin and co-workers.² Generally, in order for these compounds to be isolable at room temperature, strongly electronegative groups need to be present in the apical positions. This review deals only with transient sulfurane intermediates and does not attempt to cover those which are isolable compounds at ambient temperatures.

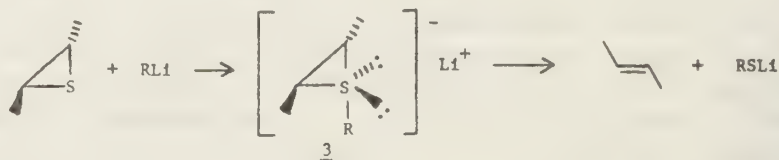
The treatment of triphenylsulfonium salts with phenyllithium has been shown to produce biphenyl and diphenylsulfide.³ Wittig and Fritz proposed tetraphenylsulfurane as an intermediate in this reaction. A benzyne route has been ruled out by isotopic labelling experiments⁴ and by the reaction of tri-*p*-tolylsulfonium fluoborate with *p*-tolyllithium⁵ in which the methyl group was retained in the *para* position in the products. Further evidence for the sulfurane intermediate may be found in the synthesis of the perfluoro analogue, tetrakis(pentafluorophenyl)sulfurane,⁶ which is stable in solution up to nearly 0°.

In their investigation of the reaction, Trost and Arndt⁷ studied the reaction of aryllithiums with S-aryldibenzothiophenium fluoborates (1). They found that electron-withdrawing groups enhanced the yield of coupling product of the aryl groups. Vinyl lithium reagents were also found to be successful in coupling; substituted styrenes were produced in quantitative yields. Alkyl lithiums do not react in the same fashion but rather give complex reaction mixtures, implying the need of a π system for coupling. Sulfurane 2 was proposed and found to collapse to the products shown. The product ratio is considered to be determined by the geometry of 2 as well as the substitution on the π system.



The desulfurization of thietanes to yield cyclopropanes has been accomplished by the formation of the thietanonium salt followed by reaction with *n*-butyllithium at -78°. ^{5b,8} Once again a sulfurane intermediate is suggested in which a sulfide is extruded to produce a 1,3-diradical followed by preferential conrotatory closure to the product. Although yields are low (20-30%) the stereospecificity is quite good (approximately 90%). The low temperatures employed account for this increase in stereospecificity over thermolysis of sulfone analogues.

When episulfides are allowed to react with lithium reagents a stereospecific elimination occurs to yield olefins and lithium mercaptides. The work of Trost and Ziman¹⁰ has ruled out an S_N2 attack at sulfur to produce a carbanion. The intermediate which would be involved was formed via another route and a loss of stereospecificity was observed. The anionic sulfurane intermediate 3 is thereby substantiated.



Dimethylsulfonium methylide has been suggested to pass through a sulfurane intermediate upon reaction with certain cyclopropenium salts to yield substituted thiophenes and biscyclopropylketones.¹¹ Similarly, some thione methylides are considered to undergo ligand exchange and coupling via sulfurane or bis-sulfurane intermediates, respectively.¹²

When triarylsulfonium halides are pyrolyzed,¹³ photolyzed,¹⁴ or allowed to react with sodium alkoxides¹⁵ to produce diaryl sulfides and aryl halides or ethers, sulfuranes and sulfuranyl radicals are again involved. The oxygen or halide stabilizes these intermediates by inductively withdrawing electron density from the hypervalent sulfur. More recently the addition of photoexcited triphenylmethyl carbanion to DMSO has been explained via an oxysulfurane intermediate.¹⁶

BIBLIOGRAPHY

1. B. M. Trost, Topics in Curr. Chem., 41, 1-31 (1973).
2. J. C. Martin and E. F. Perozzi, Science, 191, 154-9 (1976) and references cited therein.
3. G. Wittig and H. Fritz, Ann. Chem., 577, 39-46 (1952).
4. D. Harrington, J. Weston, J. Jacobus, and K. Mislow, Chem. Commun., 1079-80 (1972).
5. (a) R. W. LaRochelle and B. M. Trost, J. Am. Chem. Soc., 93, 6077-86 (1971); (b) B. M. Trost, R. W. LaRochelle, and R. C. Atkins, *ibid.*, 91, 2175-77 (1969).
6. W. A. Sheppard, *ibid.*, 93, 5597-98 (1971).
7. B. M. Trost and H. C. Arndt, *ibid.*, 95, 5288-98 (1973).
8. (a) B. M. Trost, W. L. Schinski, F. Chen, and I. B. Mantz, *ibid.*, 93, 676-84 (1971); (b) Y. H. Khim and S. Oae, Bull. Chem. Soc. Jap., 42, 1968-71 (1969).
9. (a) F. G. Bordwell, H. M. Anderson, and B. M. Pitts, J. Am. Chem. Soc., 76, 1082-85 (1954); (b) N. P. Neureiter and F. G. Bordwell, *ibid.*, 81, 578-80 (1959).
10. B. M. Trost and S. D. Ziman, J. Org. Chem., 38, 932-36 (1973).
11. B. M. Trost, R. C. Atkins, and L. Hoffman, J. Am. Chem. Soc., 95, 1285-95 (1973).
12. A. J. Arduengo and E. M. Burgess, *ibid.*, 98, 5020-21 (1976).
13. G. H. Wiegand and W. E. McEwen, J. Org. Chem., 33, 2671-75 (1968).
14. J. W. Knapczyk and W. E. McEwen, *ibid.*, 35, 2539-43 (1970).
15. J. W. Knapczyk, C. C. Lai, W. E. McEwen, J. L. Calderon, and J. J. Lubinowski, J. Am. Chem. Soc., 97, 1188-92 (1975).
16. L. M. Tolbert, *ibid.*, 100, 3952-53 (1978).

SPIROCONJUGATION: THEORETICAL VS. EXPERIMENTAL RESULTS

Reported by Terry L. Renken

April 5, 1979

A special case of homoconjugation¹ has been proposed to exist when two mutually perpendicular π systems are held together by a tetrahedral atom (i.e., Figure 1; σ and σ' are symmetry planes in D_{2d} or C_{2v} point groups). According to perturbation theory,^{2,3} direct through-space interactions can take place between appropriate orbitals, thereby leading to two new molecular orbitals, one stabilized (Figure 2a) and the other destabilized (Figure 2b). This phenomenon, termed spiroconjugation,^{2,3} should manifest itself in the properties of a large variety of molecules.⁴ This discussion, for the most part, will be limited to those spiro-polyenes for which theoretical predictions can be compared with experimental work.

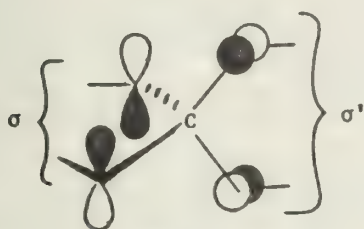


Figure 1

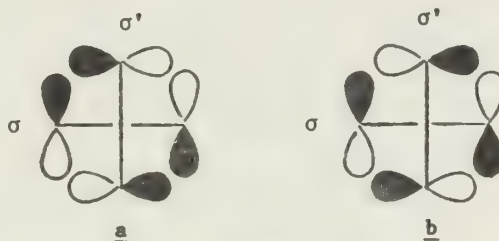
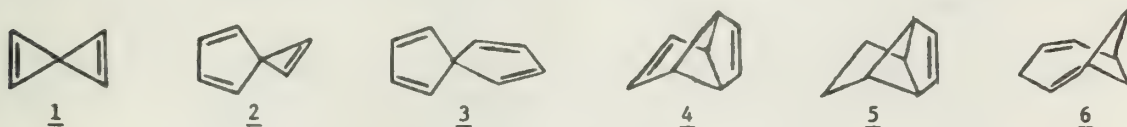


Figure 2

Calculations^{2,5,6} on the as yet unknown spiropentadiene 1 predict various degrees of spiroconjugative interaction between cyclopentene LUMO's. A photoelectron spectroscopic (PES) study⁷ of the 1,2-diethyl derivative of 2 and related model compounds compares favorably with calculations,^{6,7} though UV spectroscopic results⁸ on the same compounds are in disagreement. Spiroconjugative interaction in spiro[4.4]nonatetraene 3 was evidenced in a PES study⁹ and shifts in UV spectra^{9,10} and is in fair to excellent agreement with calculations.^{5,6,11} The reactivity¹²



of 3 in Diels-Alder reactions was explained in terms of spiroconjugation and an unfavorable transition state interaction.⁵ Photoelectron spectroscopic studies on tetravinylsilane,¹³ tetravinylmethane,¹⁴ 9,9'-spiro (9-silafluorene),¹⁵ 9,9'-spirobifluorene,¹⁵ spirobiindene,¹⁶ orthothiocarbonates,¹⁷ and various heterocyclic spirans,¹⁸ as well as electronic spectrophotometric studies of spirobiindene,¹⁹ spiro[5.5]undeca-1,4,6,9-tetraene-3,8-dione,²⁰ cyclopentadienone ketals,²¹ and thiophene-1,1-dioxide,²² all have been reported to give evidence for spiroconjugative interactions.

Recently Gleiter and co-workers²³ have proposed on the basis of model calculations that the introduction of a cyclobutane ring in place of the spiro carbon (i.e. 4) should result in a much larger interaction between π systems via through-bonds rather than through-space. Evidence for interaction between π and Walsh cyclobutane orbitals was reported in terms of the photoelectron spectra of 5²⁴ and 6²⁵ and evidence for this "relay orbital" effect was given in terms of the UV spectrum of 4.²⁶

BIBLIOGRAPHY

1. For a recent review on homoconjugation see: L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, 17, 106 (1978).
2. H. E. Simmons and T. Fukunaga, *J. Am. Chem. Soc.*, 89, 5208 (1967).
3. R. Hoffmann, A. Imamura, and G. D. Zeiss, *J. Am. Chem. Soc.*, 89, 5215 (1967).
4. H. Dürr and R. Gleiter, *Angew. Chem. Int. Ed. Engl.*, 17, 559 (1978).
5. M. G. Gordon, T. Fukunaga, and H. E. Simmons, *J. Am. Chem. Soc.*, 98, 8401 (1976).
6. J. Kao and L. Radom, *J. Am. Chem. Soc.*, 100, 760 (1978).
7. P. Bischof, R. Gleiter, H. Dürr, B. Ruge, and P. Herbst, *Chem. Ber.*, 109, 1412 (1976).
8. H. Dürr, B. Ruge, and H. Schmitz, *Angew. Chem. Int. Ed. Engl.*, 12, 577 (1973); H. Dürr and B. Ruge, *ibid.*, 11, 225 (1972); H. Dürr, B. Ruge, and B. Weiss, *Justus Liebigs Ann. Chem.*, 1150 (1974).
9. C. Batich, E. Heilbronner, E. Rommel, M. F. Semmelhack, and J. S. Foos, *J. Am. Chem. Soc.*, 96, 7662 (1974).
10. M. F. Semmelhack, J. S. Foos, and S. Katz, *J. Am. Chem. Soc.*, 94, 8637 (1972).
11. A. Tajiri and T. Nakajima, *Tetrahedron*, 27, 6089 (1971).
12. M. F. Semmelhack, J. S. Foos, and S. Katz, *J. Am. Chem. Soc.*, 95, 7325 (1973); M. F. Semmelhack, H. N. Weller, and J. S. Foos, *ibid.*, 99, 292 (1977).
13. U. Weidner and A. Schweig, *Angew. Chem. Int. Ed. Engl.*, 11, 537 (1972).
14. A. Schweig, U. Weidner, J. G. Berger, and W. Grahn, *Tetrahedron Lett.*, 557 (1973).
15. A. Schweig, U. Weidner, D. Hellwinkel, and W. Krapp, *Angew. Chem. Int. Ed. Engl.*, 12, 310 (1973).
16. A. Schweig, U. Weidner, R. K. Hill, and D. A. Cullison, *J. Am. Chem. Soc.*, 95, 5426 (1973).
17. M. Kobayashi, R. Gleiter, D. L. Coffen, H. Bock, W. Schulz, and H. Stein, *Tetrahedron*, 33, 433 (1977); A. D. Baker, M. A. Bisk, T. S. Venanzi, Y. S. Kwon, S. Sadka, and D. C. Liotta, *Tetrahedron Lett.*, 3415 (1976).
18. R. Gleiter, R. Haider, and H. Quast, *J. Chem. Res.*, 138 (1978).
19. J. H. Brewster and R. T. Prudence, *J. Am. Chem. Soc.*, 95, 1217 (1973); K. Hill and D. A. Cullison, *ibid.*, 95, 1229 (1973).
20. R. Boschi, A. S. Dreiding, and E. Heilbronner, *ibid.*, 92, 123 (1970).
21. E. W. Garbisch, Jr., and R. F. Sprecher, *ibid.*, 88, 3433, 3434 (1966); P. E. Eaton and R. A. Hudson, *ibid.*, 87, 2769 (1965); W. H. Chang, *Chem. Ind. (London)*, 709 (1964), *J. Chem. Soc.*, 2305 (1965); see also ref. 2 and 5.
22. W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, 76, 1932 (1954); F. S. Boig, G. W. Costa, and I. Osvar, *J. Org. Chem.*, 18, 775 (1953).
23. P. Bischof, R. Gleiter, and R. Haider, *J. Am. Chem. Soc.*, 100, 1036 (1978); *Angew. Chem. Int. Ed. Engl.*, 16, 110 (1977).
24. P. Bischof, R. Gleiter, M. J. Kukla, and L. A. Paquette, *J. Electron Spectrosc. Relat. Phenom.*, 4, 177 (1974).
25. R. Gleiter, P. Bischof, W. E. Volz, and L. A. Paquette, *J. Am. Chem. Soc.*, 99, 8 (1977).
26. R. Gleiter and T. Kobayashi, *Helv. Chim. Acta*, 54, 1081 (1971); H. E. Zimmerman, J. D. Robins and T. Schantl, *J. Am. Chem. Soc.*, 91, 5878 (1969); J. Meinwald and H. Tsuruta, *ibid.*, 91, 5877 (1969); 92, 2579 (1970).

ASYMMETRIC SYNTHESIS: CARBON-CARBON BOND FORMATION VIA ENAMINES, OXAZOLINES, AND RELATED COMPOUNDS

Reported by Peter Becker

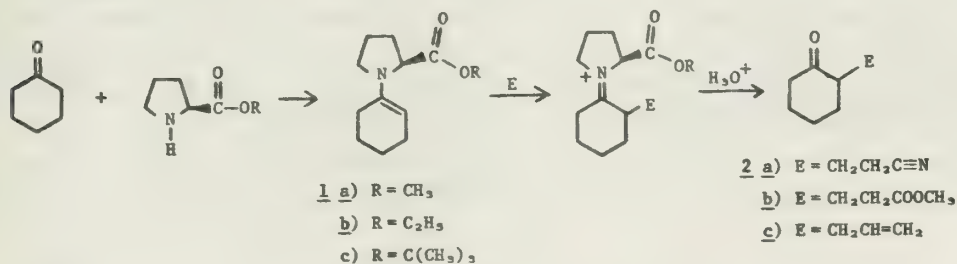
April 16, 1979

Control of the chirality of a developing asymmetric center during carbon-carbon bond formation has proven to be a major challenge. Addition of organometallic compounds to a carbonyl group, conjugate addition to α,β -unsaturated compounds, and cycloaddition were the main methods cited in the review by Morrison and Mosher of work before 1969.¹ While it is difficult to generalize, the reactions often gave optical yields of less than 40%, and these procedures did not facilitate formation of a chiral center adjacent to a carbonyl group.

Since 1969 good progress has been made in the field of asymmetric synthesis which has been reviewed by Valentine and Scott^{2,3} and in 1977 by Kagan and Fiaud.⁴ Some of the most successful asymmetric syntheses involving carbon-carbon bond formation have been accomplished using enamines, metaloenamines, oxazolines, and hydrazones. These reactions develop a chiral center adjacent to the functionalized carbon. Since these classes of compounds are carbonyl equivalents, they could be valuable for use in additional synthetic steps.

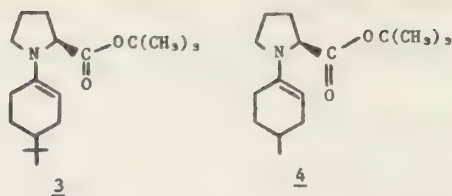
Enamines. In 1962 Stork and co-workers reported that enamines derived from secondary amines and ketones or aldehydes had been alkylated or acylated.⁵ If a chiral amine is used to form the enamine, asymmetric induction might be expected. Yamada and co-workers have made use of secondary amines derived from L-proline. Scheme I shows the alkylation of cyclohexenamines, which proceeded in variable yield.⁶

Scheme I

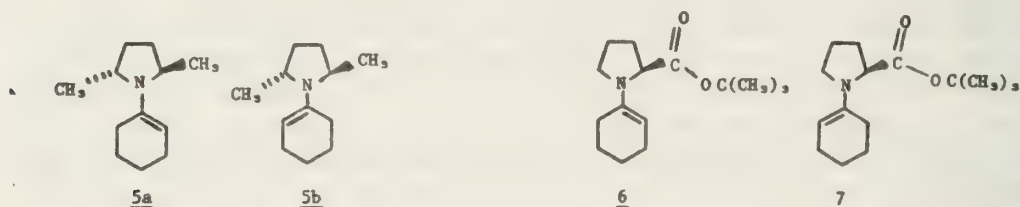


Using acrylonitrile, methyl acrylate, and allyl bromide as the electrophile (E) gave products 2 a, b, and c, respectively in moderate yield, but addition products of alkyl iodides were reported in much lower yield. Optical yields were reported as high as 59% enantiomeric excess (e.e.) in product 2b using enamine 1c; however, the chemical yield was only 17%. Generally optical yields were much lower using 1a and 1b. The problem in this reaction is that the higher temperatures and polar solvents required to achieve acceptable chemical yield drastically decrease the optical yield.

Yamada also reported alkylation of 4-substituted cyclohexanone via enamines 3 and 4.⁷ Although chemical yields were low, he found a high ratio of trans (83%) to cis (17%) products when using acrylonitrile and allyl bromide as the electrophiles.



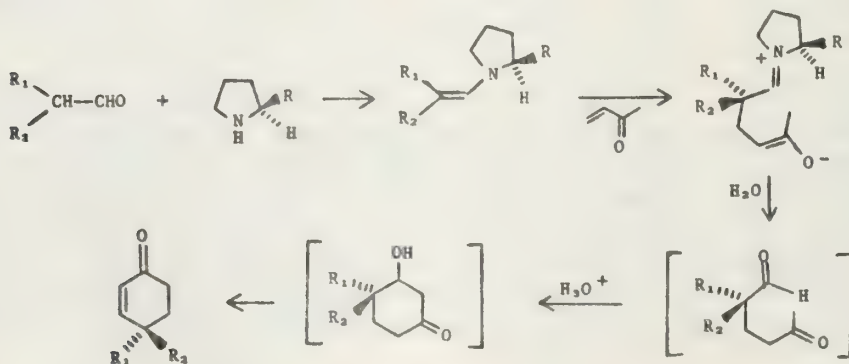
More recently Whitesell reported successful asymmetric alkylation of cyclohexanone using trans-2,5-dimethylpyrrolidine.⁸ Since this amine has a C-2 axis of symmetry, the two conformers 5a and 5b are identical. This has the advantage that a methyl group always blocks one side of the enamine. With enamines derived from proline, the rotation about the C-N bond from 6 to 7 removes the blocking group from the site of reaction. Approach from either side of conformer 7 may be expected to lead to transition states of about the same energy, so selectivity may be low.



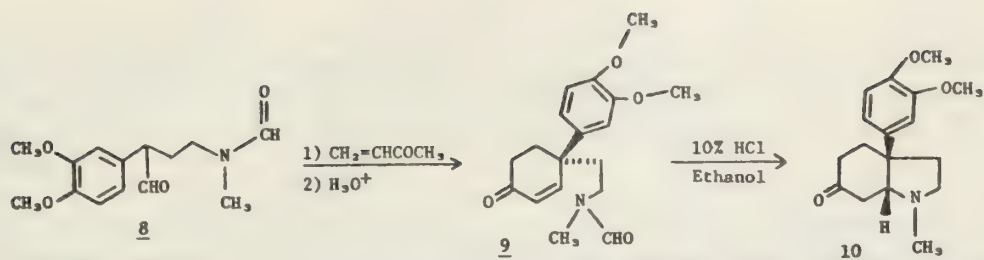
On alkylation of 5 with methyl iodide, n-propyl iodide, and allyl bromide, products were found to possess 83, 93, and 82% e.e., respectively, as determined by optical rotation. Chemical yield (50-80%) was also improved over Yamada's method.

Asymmetric synthesis of 4,4-disubstituted-2-cyclohexenones via enamines has been reported by Yamada.⁹ Observed optical rotation, not optical yield, was usually reported. A study of proline derivatives showed 2-(3-pyridylmethyl)-pyrrolidine produced the highest optical yield, 54% e.e.^{9c} Scheme II shows the reaction sequence leading to the cyclohexenones. It is important to note that R₁ or R₂ must be phenyl to produce acceptable chemical and optical yields.

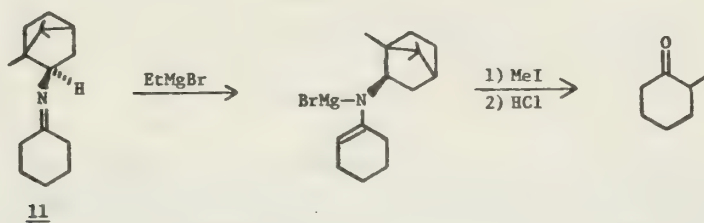
Scheme II



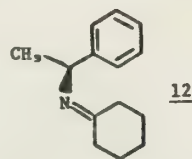
This sequence has been applied to the synthesis of (+)-Mesembrine (10).^{9d} Formation of the enamine of aldehyde 8 with L-proline pyrrolidide followed by addition of methyl vinyl ketone and hydrolysis in acetic acid/water solution gives the cyclohexenone 9 in 38% yield. Further treatment with 10% HCl in ethanol gave mesembrine (29% e.e.).



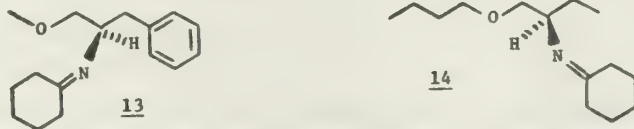
Metaloenamines. The use of metalated imines, first reported by Stork and Dowd¹⁰ has improved both optical and chemical yields of alkylations as compared to the enamine reaction. The first report of asymmetric synthesis using a metaloenamine was made by Horeau in 1968.¹¹ The isobornylimine of cyclohexanone **11** was metalated with ethylmagnesium bromide. Alkylation with methyl iodide followed by hydrolysis with hydrochloric acid gave 2-methylcyclohexanone in 72% e.e. Other alkylating agents gave lower optical yields.



Yamada reported use of optically active (S)- α -phenethyl amine and *sec*-butyl amine for asymmetric induction.¹² Metalation with lithium diisopropylamide (LDA) followed by alkylation gave poor results using *sec*-butylamine, e.g. 6% e.e. Moderate results, 26-37% e.e., were achieved with α -phenethylamine using a variety of alkylating agents.

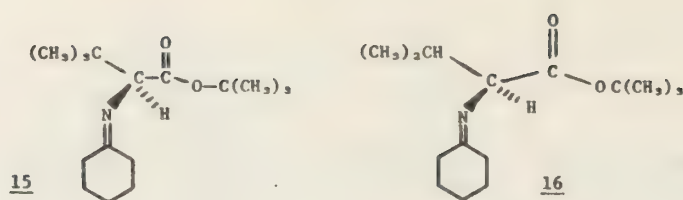


In 1976 Meyers reported an improvement on this type of synthesis.¹³ Using a chiral methoxyamine derived from *R*-phenylamine to form the cyclohexylimine **13**, it was found that metalation with LDA at -20°C followed by alkylation at -78°C gave 2-alkylcyclohexanones in 50 to 80% chemical yield with 82 to >92% e.e.



Similarly, Whitesell used a chiral amine to form the cyclohexylimine **14** which could be metalated with isopropyl magnesium bromide and alkylated with methyl iodide at -78°C .¹⁴ After hydrolysis, (R)-2-methylcyclohexanone was obtained in 81% e.e.

A variation of this method for alkylation of cyclohexanones was recently reported by Koga.¹⁵ The *t*-butyl esters of (L)-*t*-Lucine and (L)-valine were used to form imines **15** and **16**. Using LDA to form the lithio enamine, followed by alkylation with dimethylsulfate, 2-methylcyclohexanone was formed in 98% e.e. Additional examples with methyl iodide, *n*-propyliodide and allyl bromide gave products in 84-97% e.e.

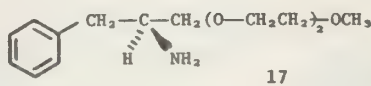


Alkylation of cyclohexanone by the procedures described is summarized in Table 1. Formation of 2,2-disubstituted cyclohexanones was also reported to proceed with high enantio selectivity (94-96% e.e.) when the initial substituent was a phenyl group.

Table 1. Asymmetric Alkylations of Cyclohexanone

Enamine or Imine	Base	Electrophile	% Yield	% e.e.	Ref.
<u>1c</u>	None	$\text{CH}_2=\text{CHCO}_2\text{CH}_3$	22	53	5
<u>1c</u>	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	20	30	6
<u>5</u>	"	CH_3I	-	83	8
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	-	82	8
<u>11</u>	$\text{C}_2\text{H}_5\text{MgBr}$	CH_3I	58	72	11
<u>12</u>	LDA	"	42	26	12
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	51	33	12
"	"	$n\text{-C}_3\text{H}_7\text{I}$	48	37	12
<u>13</u>	"	$(\text{CH}_3)_2\text{SO}_4$	72	82	13
"	"	$n\text{-C}_3\text{H}_7\text{I}$	50	>95	13
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	80	>90	13
<u>14</u>	$(\text{CH}_3)_2\text{CHMgBr}$	CH_3I	~ 58	85	14
<u>15</u>	LDA	$(\text{CH}_3)_2\text{SO}_4$	65	98	15
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	75	84	15
"	"	$n\text{-C}_3\text{H}_7\text{I}$	70	97	15
<u>16</u>	"	$(\text{CH}_3)_2\text{SO}_4$	59	84	15

Meyers and co-workers have extended the use of chiral lithio enamines to acyclic ketones¹⁶ and aldehydes. The effects of varying the base and the substituents on the chiral amine were tested in the synthesis of 2-methyloctanal.¹⁷ Using amine 17 to form the imine followed by metalation with lithium 2,2,6,6-tetramethylpiperidide and alkylation with methyl iodide gave the optimum optical yield (58%) of (S)-2-methyloctanal.



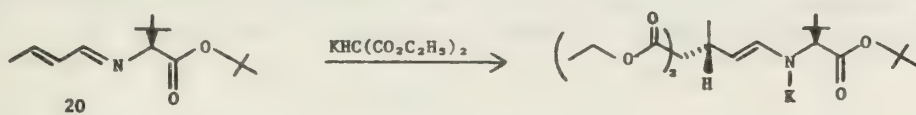
Asymmetric alkylation of ketimines proved to be more difficult under the same conditions. Kinetic control of initial proton attraction forms a mixture of the Z and E isomers 18 and 19. Alkylation at this point gives



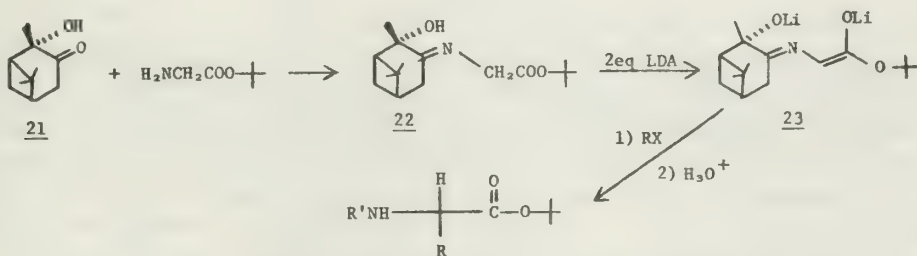
poor optical yields. Heating the lithioenamine in THF at reflux followed by cooling to -78°C allows thermodynamic control. The E isomer 19 is favored when R_2 is smaller than the amine group (Li-N-R_3), e.g. straight

chain alkyl, and optical yields of 76 to 98% e.e. are found. When R_2 is comparable in size to the amine group, e.g. benzyl or phenyl, there is little preference for 18 or 19, so low optical yields are found. Perhaps this method of equilibration would improve optical yields in the alkylation of aldehydes.

To this point all reactions described have had the asymmetric center being formed adjacent to the carbonyl. Yamada and Koga have reported formation of the chiral center at the β carbon using α,β -unsaturated aldimines.^{18,19} The *t*-butyl ester of *t*-leucine consistently provided the highest optical yields. Addition of diethyl potassium malonate to imine 20 gave 48% product in 86% e.e. Addition of a variety of Grignard reagents to 20 gave products in about 50% yield and greater than 90% e.e. It was suggested that the high enantioselectivity may be due to complexation of the organometallic with the carbonyl oxygen and the nitrogen. Attack at the β position from the side opposite the *t*-butyl group will give the products found.



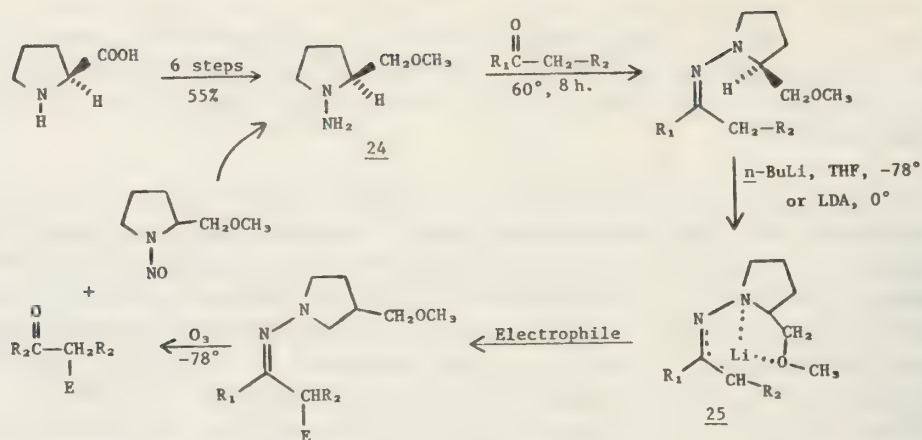
A final use of imines reverses the role of the carbonyl compound and the amine. Chiral ketone 21 and symmetric *O*-*t*-butylglycine formed imine 22 as reported by Yamada.²⁰ Treatment with 2 equivalents of LDA gives intermediate 23 which on alkylation and hydrolysis gives optically active amino acids in 66 to 83% e.e. This appears to be a reasonable route to optically active amino acids.



<u>RX</u>	<u>Yield</u>	<u>Optical Yield</u>
MeI	52%	83%
<i>i</i> -BuI	50%	83%
PhCH ₂ Br	79%	72%
3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂ Br	62%	66%

Hydrazones. Similar to enamines, chiral hydrazones have been used as the chiral auxiliary for asymmetric synthesis. Corey and Enders have shown that metalated hydrazones can function as enolate equivalents.²¹ Enders and co-workers have used chiral hydrazine, 24, a derivative of *S*-proline, in the synthesis of asymmetric α -substituted ketones^{22,23} and aldehydes.^{23,24} Scheme II shows the synthetic sequence. In this sequence it can be seen that after cleavage and reduction of the nitrosamine, the original hydrazine 24 may be recovered and reused. Dye sensitized cleavage by singlet oxygen has also been reported.²⁵

Scheme II



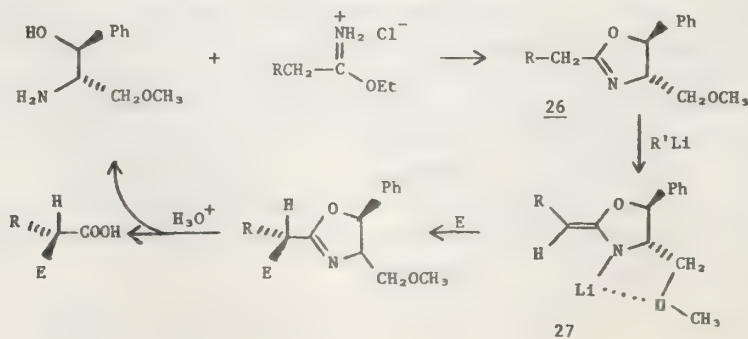
Results have been variable using this scheme for asymmetric induction as seen from the data in Table 2. The asymmetric induction in this example may be in part due to the complexation of the lithium ion with the ether oxygen and the ring nitrogen as shown in structure 25.

Table 2

Starting Compound	Electrophile	%e.e. (Conformation)	%Yield	Ref.
CH ₃ CH ₂ CHO	C ₆ H ₅ CH ₂ Br	82 (S)	62	24
CH ₃ (CH ₂) ₆ CHO	CH ₃ I	87 (R)	61	24
cyclohexanone	(CH ₃) ₂ SO ₄	85 (R)	70	22
cyclohexanone	CH ₃ CH ₂ CH ₂ I	87 (R)	73	22
acetone	CH ₃ (CH ₂) ₃ CHO	36	48	23
acetone	(CH ₃) ₂ CHCOCH ₃	47	58	23
(CH ₃) ₃ C COCH ₃	c-C ₆ H ₁₁ CHO	62	32	23

Oxazolines. The synthetic versatility of 2-oxazolines has been surveyed by Meyers and Mihelich.²⁶ Asymmetric synthesis using chiral oxazolines as intermediates has been developed rapidly in recent years by Meyers and co-workers. The work from 1974 to 1978 has been summarized by Meyers.²⁷ Scheme III outlines the general approach to the use of oxazolines in asymmetric synthesis. Synthesis of the chiral oxazoline 26 is easily achieved by the reaction of the appropriate amino alcohol and the ethyl imidate of the alkyl nitrile^{28,29} or an ortho carboxylic acid.²⁹ Treatment with base forms anion 27 which can then react with an electrophile. Hydrolysis with aqueous acid regenerates the optically active amino alcohol without racemization plus the asymmetric derivatized acid.

Scheme III

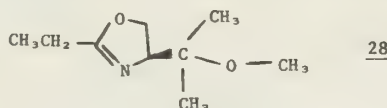


Alkylation followed by hydrolysis will give chiral carboxylic acids in good yield as seen in Table 3. Hansen reported the synthesis of (S)-2-

Table 3

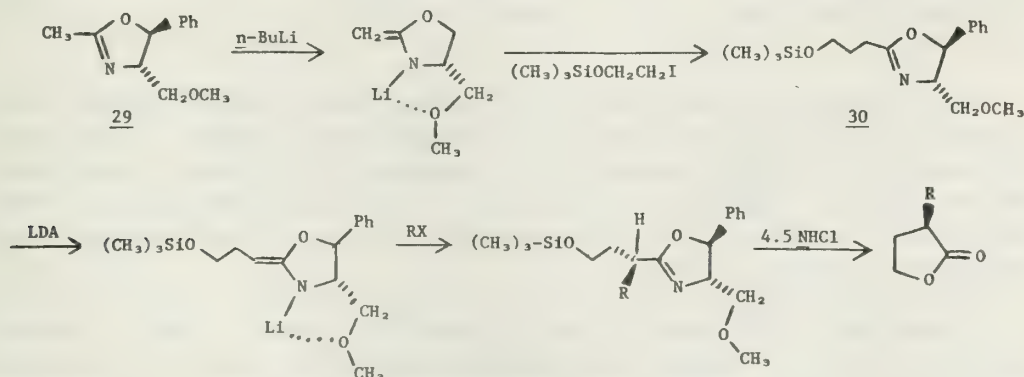
Oxazoline	Alkylating Agent	Temp.	Yield Acid	e.e. (Conf.)
1) <u>26</u> , R = CH ₃	C ₂ H ₅ I	-98	84	78 (S)
2) "	n-C ₃ H ₇ I	-98	79	72 (S)
3) "	n-C ₄ H ₉ I	-78	65	75 (S)
4) "	PhCH ₂ Cl	-78	62	74 (A)
5) <u>26</u> , R = PhCH ₂	(CH ₃) ₂ SO ₄	-98	75	78 (R)
6) <u>26</u> , R = H	(dl)-2-butylI	-65	-	34 (R)
7) "	(dl)-2-hexylI	-65	-	47 (R)
8) "	(dl)-3-octylI	-50	-	58 (R)
9) <u>28</u>	n-C ₄ H ₉ I	-98	88	75 (S)

methyl hexanoic acid in 75% e.e. using oxazoline 28.³⁰ Since this has the opposite configuration at carbon-4 from that of Meyers' oxazoline 26, one might have expected the opposite configuration in the product. This is in



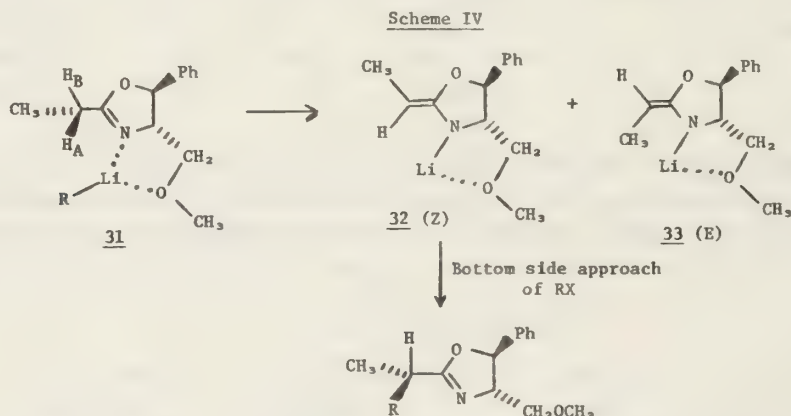
fact not the case. Use of secondary iodides to form chiral centers β to the carboxyl group has been reported.³¹ This is a kinetic resolution using an excess of racemic iodide. While perhaps not synthetically useful, this shows there is significant difference in the rates of the reactions for the two configurations of alkyl iodides.

Alkylation of oxazoline 29 with ethylene oxide followed by chlorotrimethylsilane or the equivalent, 2-trimethylsilyloxyethyl iodide, gives 30. Treatment with additional base, followed by alkylation and hydrolysis gives γ -butyrolactones in 64 to 73% e.e. and in chemical yields of 58 to 75%.³² Use of 3-trimethylsilyloxypropyl iodide similarly gives δ -valero lactones.



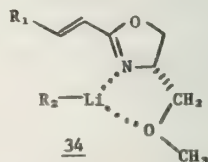
Similar to Yamada's and Koga's addition of Grignard reagents to α,β -unsaturated imines, organolithium reagents add to the β -position of α,β -unsaturated oxazolines.³³ This reaction gives products in variable yields (31 to 76%) but uniformly high optical purity (>90% e.e.). Attempts have also been made to generate chiral centers β to the oxazoline using an aldehyde as the electrophile but results have been poor (<25% e.e.).³⁴

Discerning the mechanism of these reactions and their high stereoselectivity is of interest in planning other asymmetric syntheses. The reaction proceeds in two distinct steps as shown in Scheme IV, both of which require stereoselectivity. The first step, proton abstraction, has been shown by ^{13}C NMR spectroscopy to give a 9:1 ratio of Z (32) to E (33) products.³⁵ Meyers has proposed that the lithium initially complexes with the methoxy oxygen and the ring nitrogen. Decrease in selectivity when the methoxymethyl group is replaced by methyl supports this proposition.³⁶ To relieve crowding the ethyl group is largely in the conformation shown in structure 31. Removal of H_A then gives the Z geometry.



The second step, alkylation, must also be selective. Meyers has shown that if the phenyl group is replaced with methyl or hydrogen, the selectivity falls greatly.³⁶ The opposite configuration yet high selectivity found using oxazoline 28 might suggest that the first step proceeds as described above. The dimethylmethoxymethyl group is sufficiently bulky to block bottom side approach of the alkylation agent just as the phenyl group blocks topside approach in oxazoline 31.

Addition to the β carbon by nucleophilic attack takes place in only one step and occurs in high optical yield even in the absence of the phenyl group.^{33a} This suggests a complex such as 34 may lead to the transition state.



Conclusion. These compounds, oxazolines, enamines, and related species provide useful means of asymmetric synthesis. They can be used to generate a chiral center while leaving the carbonyl function or equivalent in tact. Another important consideration is the ease with which the chiral auxiliary can be recovered. This allows repeated use and is an economical factor, too.

From these studies it can be seen that steric factors remain important but also that intramolecular complexation as a means of control is important. Since the metaloenamines and oxazolines that contain ether oxygens employ both factors, they appear at this time to be the most promising means for successful asymmetric syntheses of ketones, aldehydes, and carboxylic acids. Perhaps additional refinements of the procedures using these compounds will allow consistent results with optical yields greater than 90%.

BIBLIOGRAPHY

1. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971.
2. J. W. Scott and D. Valentine, Jr., *Science*, 184, 943 (1974).
3. D. Valentine, Jr., and J. W. Scott, *Synthesis*, 329 (1978).
4. H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 10, (1977).
5. G. Stork, A. Brizzolara, H. Landesman, J. Szmuzkovic, and R. Terrell, *J. Am. Chem. Soc.*, 85, 207 (1962).
6. (a) S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Lett.*, 4233 (1969); (b) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, 20, 246 (1972).
7. K. Hiroi and S. Yamada, *Chem. Pharm. Bull.*, 21, 47 (1973).
8. J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, 42, 1663 (1977).
9. (a) S. Yamada and G. Otani, *Tetrahedron Lett.*, 4237 (1969); (b) G. Otani and S. Yamada, *Chem. Pharm. Bull.*, 21, 2112 (1973); (c) T. Sone, K. Hiroi, and S. Yamada, *ibid.*, 21, 2331 (1973); (d) G. Otani and S. Yamada, *ibid.*, 21, 2130 (1973).
10. G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, 85, 2178 (1962).
11. D. Meá-Jacheet and A. C. Horeau, *Bull. Soc. Chim. Fr.*, 4571 (1968).
12. M. Kitamoto, K. Hiroi, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.*, 22, 459 (1974).
13. A. I. Meyers, D. R. Williams, and M. Druehlinger, *J. Am. Chem. Soc.*, 98, 3032 (1976).
14. J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, 42, 377 (1977).
15. S. Hashimoto and K. Koga, *Tetrahedron Lett.*, 573 (1978).
16. A. I. Meyers and D. R. Williams, *J. Org. Chem.*, 43, 3245 (1978).
17. A. I. Meyers, G. S. Poindexter, and Z. Brich, *ibid.*, 43, 892 (1978).
18. S. Hashimoto, S. Yamada, and K. Koga, *J. Am. Chem. Soc.*, 98, 7450 (1976).
19. S. Hashimoto, N. Komeshima, S. Yamada, and K. Koga, *Tetrahedron Lett.*, 2907 (1977).
20. S. Yamada, T. Oguri, and T. Shori, *J. Chem. Soc., Chem. Commun.*, 136 (1976).
21. E. J. Corey and D. Enders, *Chem. Ber.*, 111, 1337, 1362 (1978).
22. D. Enders and H. Eichenauer, *Angew. Chem. Int. Ed. Eng.*, 15, 549 (1976).
23. H. Eichenauer, E. Friedrich, W. Lutz, and D. Enders, *Angew. Chem. Int. Ed. Eng.*, 17, 206 (1978).
24. D. Enders and H. Eichenauer, *Tetrahedron Lett.*, 191 (1977).
25. E. Friedrich, W. Lutz, H. Eichenauer, and D. Enders, *Synthesis*, 893 (1977).
26. A. I. Meyers and E. D. Mihelich, *Angew. Chem. Int. Ed. Eng.*, 15, 270 (1976).
27. A. I. Meyers, *Acct. Chem. Res.*, 11, 375 (1978).
28. A. W. Dox, *Org. Syn. collected Vol. 1*, p. 5 (1942).
29. (a) A. I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc.*, 96, 268 (1974); (b) A. I. Meyers and G. Knaus, *ibid.*, 96, 6508 (1974); (c) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *ibid.*, 98, 567 (1976).
30. J. F. Hansen and C. S. Cooper, *J. Org. Chem.*, 41, 3219 (1976).
31. (a) A. I. Meyers and K. Kamata, *J. Am. Chem. Soc.*, 98, 2290 (1976); (b) A. I. Meyers and K. Kamata, *J. Org. Chem.*, 39, 1603 (1974).
32. A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, 40, 1186 (1975).
33. (a) A. I. Meyers and C. E. Whitten, *Heterocycles*, 4, 1687 (1976); (b) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, 97, 6266 (1975).
34. A. I. Meyers and G. Knaus, *Tetrahedron Lett.*, 1333 (1974).
35. (a) M. A. Hoobler, D. E. Berbreiter, and M. Newcombe, *J. Am. Chem. Soc.*, 100, 8182 (1978); (b) A. I. Meyers, E. S. Snyder, and J. J. H. Ackerman, *ibid.*, 100, 8186 (1978).
36. A. I. Meyers, A. Mazzu, and C. E. Whitten, *Heterocycles*, 6, 971 (1977).

ENZYME STEREOSPECIFICITY IN BIOSYNTHESIS

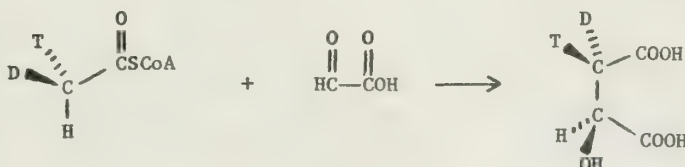
Reported by Peter Senter

April 19, 1979

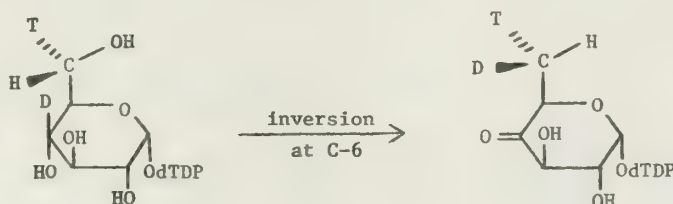
A great number of enzymatic reactions involve the reaction of achiral, torsionally symmetric functionalities such as methyl or phosphate groups. Since free rotation is possible about the bond joining a methyl or a phosphate group to the rest of the molecule, no discrimination is possible between the three terminal atoms. However, enzymatic reactions at a methyl or a phosphate group may proceed with stereospecificity, resulting in a definite spatial relationship between the group that becomes attached and the atom which it displaces.

In order to determine the stereochemistry involving methyl group transformations, it is necessary to prepare methyl groups of known configuration using all three isotopes of hydrogen. Several methods for the synthesis of chiral acetic acid have been established.^{1,2} The acetic acids thus prepared contain tracer levels of tritium, and therefore only a small fraction of the molecules are chiral.

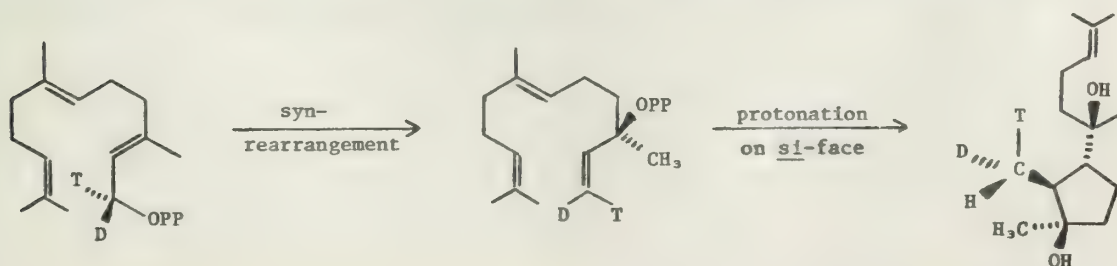
An assay which can unequivocally establish the stereochemistry of chiral acetic acid has been reported.¹ Using this procedure it is possible to deduce the stereochemistry of a reaction in which an asymmetric methyl group is produced. This assay has established that malate synthase reacts with inversion of stereochemistry at the methyl group in acetyl coenzyme A.¹



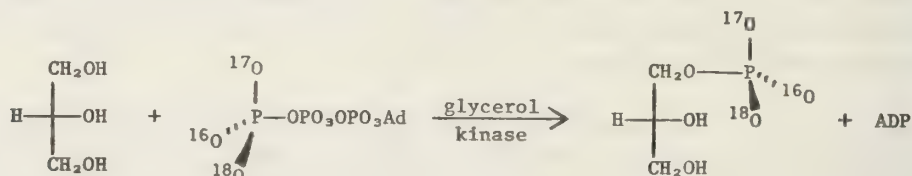
The stereochemistry of dTDP-glucose oxidoreductase proceeds with inversion of stereochemistry at the C-6 hydroxymethyl group in dTDP-glucose.³



The stereochemical ambiguities present in cyclonerodiol biosynthesis have been resolved by the determination of the chirality of a methyl group produced on protonation of labeled nerolidyl pyrophosphate.⁴



Until very recently it has not been possible to investigate the stereochemistry of enzymatic reactions on phosphorous due to the unavailability of chiral phosphate. However, methods for the preparation and stereochemical analysis of chiral phosphorothioates,⁵ and chiral phosphates having all three stable isotopes of oxygen,⁶ have been reported. A synthesis of $[\gamma\text{-}^{16}\text{O}, ^{17}\text{O}, ^{18}\text{O}]\text{ATP}$ of known configuration has recently been accomplished.^{6c} This labeled ATP has been used to demonstrate that glycerol is phosphorylated by glycerol kinase with inversion of stereochemistry at phosphorous.



In addition to all of the interesting chemistry that has evolved from research dealing with chiral methyl and phosphate groups, a great deal has been learned about the active sites of enzymes, enzyme stereospecificity, and mechanisms of enzyme mediated reactions.

BIBLIOGRAPHY

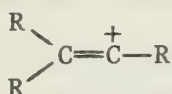
1. (a) J. W. Cornforth, J. W. Redmond, E. Eggerer, W. Buckel, and C. Gutschow, *Eur. J. Biochem.*, **14**, 1 (1970); (b) J. Luthy, J. Retey, and D. Arigoni, *Nature*, **221**, 1213 (1969).
2. (a) H. Lenz, W. Buckel, P. Wunderwald, G. Biedermann, V. Buschmeier, H. Eggerer, J. W. Cornforth, J. W. Redmond, and R. Mallaby, *Eur. J. Biochem.*, **24**, 207 (1971); (b) C. A. Townsend, T. Scholl, and D. Arigoni, *J. Chem. Soc., Chem. Commun.*, 921 (1975); (c) A. Kraus, W. Dessau, and H. Simon, *Z. Physiol. Chem.*, **357**, 1209 (1976); (d) E. Caspi and C. E. Eck, *J. Org. Chem.*, **42**, 767 (1977); (e) M. Kajiwara, S. F. Lee, A. I. Scott, M. Akhtar, C. R. Jones, and P. M. Jordan, *J. Chem. Soc., Chem. Commun.*, 967 (1978).
3. (a) C. E. Snipes, G. U. Brillinger, L. Sellers, L. Mascaro, and H. G. Floss, *J. Biol. Chem.*, **252**, 8113 (1977); (b) C. E. Snipes, C. J. Chang, and H. G. Floss, *J. Am. Chem. Soc.*, **101**, 701 (1979).
4. (a) D. E. Cane and M. S. Shiao, *J. Am. Chem. Soc.*, **100**, 3203 (1978); (b) D. E. Cane and R. Iyengar, *ibid.*, **100**, 3256 (1978); (c) D. E. Cane, R. Iyengar, and M. S. Shiao, *ibid.*, **100**, 7122 (1978); (d) D. E. Cane and R. Iyengar, *ibid.*, in press.
5. For leading references see: (a) P. M. Burgers and F. Eckstein, *Proc. Natl. Acad. Sci., U.S.A.*, **75**, 4798 (1978); (b) J. P. Richard, H. T. Ho, and P. A. Frey, *J. Am. Chem. Soc.*, **100**, 7756 (1978).
6. (a) S. R. Jones, L. A. Kindman, and J. R. Knowles, *Nature*, **275**, 564 (1978); (b) S. J. Abbott, S. R. Jones, S. A. Weinman, and J. R. Knowles, *J. Am. Chem. Soc.*, **100**, 2558 (1978); (c) W. A. Blattler and J. R. Knowles, *ibid.*, **101**, 510 (1979); (d) P. M. Cullis and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 512 (1978).

GENERATION AND UTILITY OF VINYLIC CARBOCATIONS

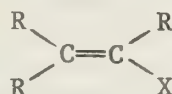
Reported by Michael W. Robertson

April 23, 1979

The existence of vinyl cations, 1, as discrete reactive intermediates is now well documented.^{1,2} Early mechanistic investigations on reactions such as electrophilic addition to alkynes and allenes suggested the intermediacy of these disubstituted carbenium ions.^{1a-c} A more definitive account of the chemistry of 1 has recently appeared^{2a} as a result of reports on the solvolytic generation of 1 via bond heterolysis of vinyl substrates 2. This report will summarize recent methods for the generation of 1 with applications in organic synthesis.³



1



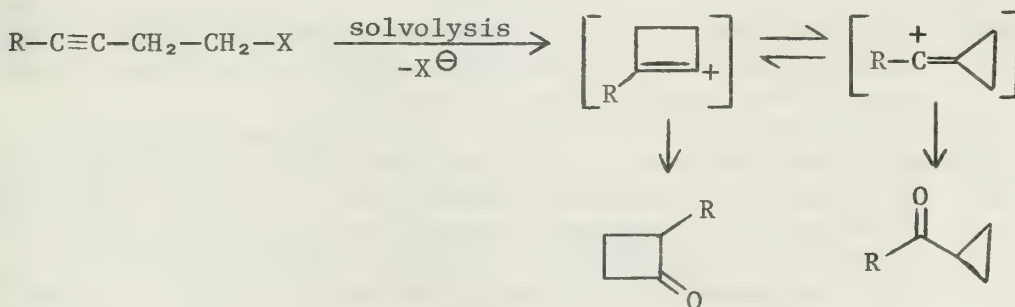
2a X = OSO₂R

2b X = OSO₂R_F

2c X = halide

Vinyl cations have been postulated as intermediates in intermolecular electrophilic addition to arylsubstituted acetylenes.⁴⁻⁶ Depending upon the nucleophile present, synthetically useful yields of ketones⁷ and 1,1,3,3-tetrasubstituted cyclobutanes⁸ have been achieved. Several examples of intramolecular electrophilic addition to acetylenes have appeared. The "homo-propargylic rearrangement" (Scheme I) offers high yields of cyclobutanones and cyclopropyl ketones,^{2b,9} depending on the nature of the R substituent and reaction conditions. Transannular cyclization reactions of acetylenic halides¹² and biomimetic cyclization¹³ have both been proposed to occur via a vinyl cation intermediate.

Scheme I



Intermolecular electrophilic addition to allenes usually gives rise to a complex product mixture,^{1b,2b} whereas intramolecular additions ("homo-allenyl rearrangement") have shown preparative utility in the synthesis of cyclopropyl ketones¹⁰ and 2-octalones.¹¹

The generation of vinyl cations by solvolysis of vinylic substrates 2 is now widely accepted.¹⁴⁻¹⁶ This heterolytic process is possible only if two conditions are observed: (a) powerful leaving groups such as triflate or nonaflate are used or (b) there is stabilization of the resultant cation by electron releasing α -substituents. In the latter case, chloride¹⁷ and even fluoride¹⁸ have been shown to be acceptable leaving groups in vinyl cation generation. Recently, considerable attention has

been directed toward Friedel-Crafts alkylation via carbenium ions derived from 2.¹⁹ The synthetic scope of this reaction appears to be limited by the ability of 2 to undergo elimination as well as the rather harsh reaction conditions.^{19b} Intramolecular Friedel-Crafts alkylation in the synthesis of various heterocycles via the intermediacy of 1 has also been reported.²⁰

BIBLIOGRAPHY

1. (a) L. R. Subramanian and M. Hanack, *J. Chem. Ed.*, 52, 80 (1975); (b) P. J. Stang, *Prog. Phys. Org. Chem.*, 10, 205 (1973); (c) G. Modena and V. Tonellato, *Adv. Phys. Org. Chem.*, 9, 185 (1971); (d) M. Hanack, *Acc. Chem. Res.*, 9, 364 (1976); (e) Z. Rappoport, *ibid.*, 9, 265 (1976).
2. (a) P. Stang, *Acc. Chem. Res.*, 11, 107 (1978); (b) M. Hanack, *Angew. Chem. Int. Ed. Eng.*, 17, 333 (1978).
3. (a) S. A. McNeely and P. J. Kropp, *J. Am. Chem. Soc.*, 98, 4319 (1976); (b) C. A. Grob and P. Wenk, *Tetrahedron Lett.*, 4195 (1976).
4. R. C. Fahey, M. T. Payne, and D. J. Lee, *J. Org. Chem.*, 39, 1124 (1974).
5. F. Marcuzzi and G. Melloni, *J. Am. Chem. Soc.*, 98, 3295 (1975).
6. D. Kaufmann and R. Kupper, *J. Org. Chem.*, 39, 1428 (1974).
7. (a) R. W. Bott, C. Eaboin, and D. R. M. Walton, *J. Chem. Soc.*, 384 (1965); (b) D. S. Noyce, *et al.*, *J. Am. Chem. Soc.*, 87, 2295 (1965); (c) D. S. Noyce and M. D. Schiavelli, *ibid.*, 90, 1020 (1968).
8. K. Griesbaum and W. Seiter, *J. Org. Chem.*, 41, 937 (1976) and references cited therein.
9. (a) M. Hanack, J. Häffner, and I. Herterich, *Tetrahedron Lett.*, 875 (1965); (b) C. J. Collins, B. Benjamin, H. Stutz, and M. Hanack, *J. Am. Chem. Soc.*, 99, 1669 (1977); (c) M. Hanack, *et al.*, *Org. Synth.*, 54, 84 (1974); (d) H. Stutz and M. Hanack, *Tetrahedron Lett.*, 2457 (1974).
10. (a) M. Bertrand, *Bull. Soc. Chim. Fr.*, 3044 (1968); (b) M. Hanack and J. Häffner, *Tetrahedron Lett.*, 2191 (1964).
11. K. Harding, J. Cooper, and P. Puckett, *J. Am. Chem. Soc.*, 100, 993 (1978).
12. (a) M. J. Chandy, L. R. Subramanian, and M. Hanack, *Chem. Ber.*, 108, 2212 (1975); (b) Ref. 38 in ref. 2b; (c) C. E. Harding and M. Hanack, *Tetrahedron Lett.*, 1253 (1977).
13. W. S. Johnson, *Angew. Chem. Int. Ed. Eng.*, 15, 9 (1976).
14. (a) C. A. Grob and H. R. Pfaendler, *Helv. Chim. Acta*, 54, 2060 (1971); (b) L. L. Miller and D. A. Kaufman, *J. Am. Chem. Soc.*, 90, 7282 (1968); (c) Z. Rappoport and A. Gal, *ibid.*, 91, 5246 (1969); (d) P. Stang and R. Summerville, *ibid.*, 91, 4600 (1969).
15. L. J. Adzina, U. of Illinois Seminar, 167 (1974) and references cited therein.
16. See references 1 and 2 and references cited therein.
17. Z. Rappoport, P. Shulman and M. T. Shoolman, *J. Am. Chem. Soc.*, 100, 7041 (1978).
18. L. Eckes and M. Hanack, *Chem. Ber.*, 111, 1253 (1978).
19. (a) R. M. Roberts and M. B. Abdel-Baset, *J. Org. Chem.*, 41, 1698 (1976); (b) P. J. Stang and A. B. Anderson, *J. Am. Chem. Soc.*, 100, 1520 (1978).
20. (a) T. Sonoda *et al.*, *J. Chem. Soc. Chem. Commun.*, 612 (1976); (b) T. Sonoda *et al.*, *Bull. Chem. Soc. Jap.*, 49, 2560 (1976); (c) F. Marcuzzi and G. Molloni, *Tetrahedron Lett.*, 2771 (1975).

SEPARATION OF STERIC AND POLAR EFFECTS

Reported by Rick Gdanski

April 26, 1979

Inspired by the work of other chemists,^{1a} L. P. Hammett, in 1937,^{1b} published a treatment which successfully related chemical structures of benzene derivatives with reactivity. Physical organic chemists have since attempted to use similar relationships to relate structure with reactivity. Such treatments, including the Hammett equation, are called Linear Free Energy Relationships (LFER). Correlation of pKa's, rate constants, NMR shifts,² and other spectroscopic data³ with structure in search of LFER's have met with variable success. Taft, in 1952, published a method of quantitative separation of the effects of structure on reactivity into polar, steric, and resonance (or mesomeric) contributions.⁴ Though many data have been correlated by the substituent constants derived from this treatment,⁵ assumptions on which the treatment was based have been criticized. The subsequent development of Taft's approach by Marvin Charton is the subject of this review. Nonetheless, Taft's work was a major step forward in the elucidation of the relationships of structure with reactivity. Therefore, a brief review of his work is in order before describing alternative approaches to an analysis of the effects of structure on reactivity.

In his excellent review on the separation of polar, steric, and resonance effects, Taft⁴ uses thermodynamics and transition state theory to describe the effect of substituents on the free energies of activation of reactions. However, he points out that such a treatment does not allow one to separate the various effects of substituents. Therefore, data must be accumulated in which an observable is a function of only one effect or in which all other effects are constant. Ingold suggested,⁶ in 1930, that the basic hydrolysis of aliphatic esters $\text{RCO}_2\text{R}'$ could be used to determine the "polarity" of substituents. Taft later suggested that the acidic hydrolysis could be used as a measure of steric effects only and that the basic hydrolysis could be used in conjunction with the acidic hydrolysis as a measure of polar effects. Resonance effects could be completely ignored if one used saturated substituents since the transition state of the hydrolyses can be approximated as saturated⁷ also.

This treatment required three assumptions: (1) the relative free energies of activation may be treated as the sum of independent contributions from polar, steric, and resonance effects; (2) in the corresponding acidic and basic reactions, the steric and resonance effects are the same; and (3) the polar effects are markedly greater in the basic than in the acidic series. Thus, his steric parameter E_s is defined by Equation 1 and his polar parameter σ^* is defined by Equation 2, where k is the rate constant of a C-substituted ester, k_0 is the rate constant of the $\text{MeCO}_2\text{R}'$ ester, and B and A correspond to basic and acidic hydrolysis, respectively.

$$E_s = \log \left[\frac{k}{k_0} \right]_A \quad (1)$$

$$\sigma^* \equiv \left[\frac{1}{2.48} \right] \left[\log \left[\frac{k}{k_0} \right]_B - \log \left[\frac{k}{k_0} \right]_A \right] \quad (2)$$

R' remains constant throughout a given series. The constant 2.48 is an attempt to put the σ^* constants on the same scale as the Hammett σ

constants. Taft later⁸ used the constant 5.51 in place of 2.48 to define a set of σ_I constants that would be on a proper scale with σ_p such that $\sigma_R = \sigma_p - \sigma_I$, where σ_p is for para Hammett σ 's and σ_R is the resonance contribution to σ_p .⁹ Table 1 lists a few E_s , σ^* , and σ_I values.

The first assumption is not necessarily self-evident and has received only slight criticism⁵ since this approximation is required if any progress is to be made at all. The second assumption is the heart of the treatment and is the subject of a large amount of criticism. Taft argued that the transition states for the two reaction series differ only by two protons and that their steric requirements are negligible. However, some workers feel that steric inhibition of solvation is different in the two series because of the opposite charges in the corresponding transition states.¹⁰ Most workers agree that the resonance effects are the same since the transition states are saturated and only saturated substituents are used in the treatment for E_s values. The third assumption remains valid on the grounds of the hydrolyses of p- and m- substituted benzoic esters. For the basic series, ρ is generally between +2.2 and +2.8 while for the acidic series, ρ is between -0.2 and +0.5.¹¹

The general use of Taft's E_s values and σ^* values has met with reasonable success.⁵ However, there exist many cases in which correlations are very poor or in which outlying data points cannot be easily accounted for.¹² Such cases constitute grounds for re-examination of Taft's derivation and his substituent constants. The major criticism of his work lies on the validity of his σ^* constants for alkyl groups. Much evidence has been accumulated that indicates the inductive effects of alkyl groups are constant and very near zero relative to hydrogen¹³ and that the observed effects are the result of alkyl polarizability.¹⁴ Another criticism is his procedure of defining E_s and σ^* values from the average of values determined from different reactions and in various solvents at different temperatures. This procedure has made it difficult to define new values that are on the same scale as the original values.

The most thorough re-examination of Taft's work is that of M. Charton. He first correlated E_s constants for six symmetrical substituents with the van der Waals radii r_v using Equation 3.¹⁵ The regression constant ψ is a

$$E_s = \psi r_v + h \quad (3)$$

measure of the dependence of E_s on r_v . The results of the correlation were $\psi = -2.33$, $h = 3.99$, and correlation coefficient $r = 0.996$ and indicate that E_s is indeed a steric substituent constant. Charton preferred to define a new steric parameter v from Equation 4 and calculated v values

$$v_x \equiv r_{v,x} - r_{v,H} = r_{v,x} - 1.20 \quad (4)$$

for twelve symmetrical substituents.¹⁶ He used Equation 5 to correlate the rate constants of six sets of acid-catalyzed esterification reactions

$$\log k = \psi v + h \quad (5)$$

with five v constants having values ranging from 0.00 to 1.56. The regression constant ψ is defined as a steric reaction constant. The sets contained only three or four data points each that were symmetrical, but these data give correlation coefficients ranging from 0.9990 to 0.9999.

The remaining data in the sets were used to define ν values for 42 unsymmetrical groups. Table 1 lists a few of these values. These ν values were correlated with 173 rate constants in 22 sets of esterification acid-catalyzed hydrolysis of esters, and acid-catalyzed alcoholysis of esters. The sets contained from 3 to 26 data points and had correlation coefficients ranging from 0.975 to 0.99995. The sets contained a total of 31 different substituents having ν values ranging from 0.00 for H to 1.70 for (*i*-Bu)₂CH. They included 6 different solvent systems and varied in temperature from 20 to 80°C. The success of these estimated ν values to correlate the wide range of conditions without the use of average ν values suggests that they are pure steric parameters and are an improvement over Taft's E_s values. The results also showed that the ψ 's for four of the sets used in Taft's treatment were significantly different from each other. This dictates that average E_s values defined from these sets must have significant error.

Table 1

Substituent	r_ν	E_s	ν	σ^*	σ_I
H	1.20	1.24	0.00	0.490	0.00 [†]
Me	1.715	0.00	0.52	0.000	-0.05 [†]
Et		-0.07	0.56	-0.100	-0.05 [†]
Pr		-0.36	0.68	-0.115	-0.03
<i>i</i> -Pr		-0.47	0.76	-0.190	-0.03
Bu		-0.39	0.68	-0.130	-0.04
<i>i</i> -Bu		-0.93	0.98	-0.125	-0.03
<i>s</i> -Bu		-1.13	1.02	-0.210	-0.03
<i>t</i> -Bu	2.435	-1.54	1.24	-0.300	-0.07 [†]
CF ₃	2.107	-1.16	0.91		0.42
CCl ₃	2.579	-2.06	1.38	2.65	0.43
CBr ₃	2.760	-2.43	1.56		
CI ₃	2.988		1.79		
MeO			0.36		0.25 [†]
PrO			0.56		0.27
<i>s</i> -BuO			0.86		0.26
Me ₃ Si	2.60		1.40		-0.13
F	1.47		0.27		0.52 [†]
Br	1.85		0.65		0.45 [†]

[†]Denotes Taft's original σ_I values.

Charton proceeded to show that the steric effects in base-catalyzed ester hydrolysis ψ_B are not the same as for the acid-catalyzed hydrolysis ψ_A .¹⁷ For nine sets of acid-base hydrolysis pairs containing only alkyl substituents and in which inductive effects were considered to be unimportant, he found that ψ_B was significantly larger (more negative) than ψ_A .

This result contradicts the prediction that ψ_A would be larger on the basis that the transition state for the acid-catalyzed hydrolysis contains two extra protons. It has been suggested that this discrepancy arises either from differences in solvation of the two transition states or in the positions of the two transition states. In either case, Taft's σ^* constants will be subject to some error, especially for those substituents with small values (*i.e.*, alkyl groups). This work undermines Taft's second assumption and thereby questions the validity of the σ^* constants for alkyl groups.

Charton then found that ψ_B and ψ_A for the hydrolysis of C-substituted amides were the same¹⁸ and used these data to define sets of σ^* constants for alkyl groups at three different temperatures¹⁸ using Equation 2. The data used were obtained in the same solvent and in the same laboratory. These σ^* constants were found to have no dependence on structure and had little relationship with one another or with Taft's values. This lead Charton to the conclusion that "the Taft σ^* values for alkyl groups are artifacts."

As an alternative approach to defining inductive or polar substituent constants σ_I , Charton correlated selected pKa's of substituted acetic acids with Taft's σ_I values.¹⁹ From the regression equation defined by this correlation, Charton defined a large number of σ_I constants. Table 1 lists a few of these values. The values marked with an \dagger are Taft's original values.⁸ This method has the advantages of being more reliable in the pKa determinations, is essentially insensitive to steric effects, requires measurement of only one number, and avoids Taft's second assumption.

Charton has also defined steric parameters for alkoxy groups ν_{ox} ,²⁰ alkyl- and dialkylamino groups $\nu_{Nx^1x^2}$,²¹ and alkylthio groups ν_{sx} .²² Many of these constants were defined in base-catalyzed reactions where the electrical effects of the alkyl groups were assumed to be constant. Since this assumption is not universally accepted,²³ its validity is in question. Nonetheless, a set of fifteen rate constants for the basic hydrolysis of ZCO_2X esters (Z and X are alkyl only) in 40% aqueous dioxane at 35°C were correlated²⁰ with Equation 6 with the following results: $\psi_1 = -2.06$, s.d. 0.0805; $\psi_2 = -2.54$, s.d. 0.0741; $h = 3.23$, s.d. 0.0822; $r = 0.995$. Independent researchers have correlated ΔG^\ddagger of rotation of N,N-dimethylamides,²⁴ base-catalyzed hydrolysis of p-

$$\log k = \psi_1 \nu_Z + \psi_2 \nu_{ox} + h \quad (6)$$

nitrophenyl esters,²⁵ and base-catalyzed hydrolysis of alkyl carboxylates²⁶ with Charton ν constants and Taft-Charton σ_I constants with excellent results. In cases where the E_s constants were also correlated,^{24,26} the ν constants were found to be as good or better than the E_s constants.

To show the utility and validity of the ν , σ_I , and σ_R constants ($\sigma_R = \sigma_p - \sigma_I$), Charton has re-examined several phenomena in which steric versus electronic effects are unclear and has obtained results which occasionally contradict longstanding ideas. In general his analysis is started by correlation of an observable Q_x with Equation 7. The coefficients α , β , and ψ are subjected to "Student t" tests for significance. The terms found to be insignificant are dropped and the data correlated

$$Q_x = \alpha \sigma_{I,x} + \beta \sigma_{R,x} + \psi \nu_x + h \quad (7)$$

with the remaining terms. Using this method, Charton has found that: (1) Taft's ortho steric substituent constants E_s^o are completely accounted for by σ_I and σ_R ,¹⁵ a result which completely contradicts the definition of E_s^o ;⁴ (2) rate constants for E2 elimination of β -alkyl-substituted 'onium compounds were found to be completely accounted for by ν ,²⁷ suggesting that the electrical effects of the alkyl groups are at least constant and that steric hindrance is the major effect of alkyl groups on the rate constants; (3) the orientation of E1 and E2 eliminations for three sets of alkyl bromides and three sets of alkyl brosylates were found to be completely accounted for by steric effects in five of the six sets;²⁷ (4) for the half-lives of racemization of 2-nitro-6-carboxy-2'-methoxybiphenyls substituted in either the 3', 4', or 5' position,²⁸ the 3' substituents exert predominantly a steric effect which has been attributed to "buttressing", the 4' substituents exert an electrical effect that is both inductive and mesomeric and shows no steric effect, and the 5' substituents exert only inductive effects.

To allow estimation of ν constants, Charton has correlated 39 ν constants for alkyl groups with the number of α , β and γ carbon atoms from the first carbon atom in the alkyl group with Equation 8.²⁹ The results are $a = 0.497$, s.d. 0.0230; $b = 0.409$, s.d. 0.0199; $c = 0.0608$, s.d. 0.0118; $i = -0.309$, s.d. 0.0457; $r = 0.986$. Since this correlation was successful,

$$\nu = a n_{\alpha} + b n_{\beta} + c n_{\gamma} + i \quad (8)$$

it suggests the possibility of correlating rate constants in a similar fashion using Equation 9. Thus, Charton has correlated the rate constants for nucleophilic substitution of benzyl chloride by alkoxide ions (set 1)

$$Q_x = a' n_{\alpha} + b' n_{\beta} + c' n_{\gamma} + i' \quad (9)$$

and of 1-chloro-2,4-dinitrobenzene by alkylamines (set 2), of alkaline hydrolysis of ethyl 4-nitrophenyl alkyl phosphonates (set 3), C-substituted amides (set 4), and dialkylphenylacetoneitriles (set 5), of the reaction of alcohols with 4-nitrobenzoylchloride (set 6), and of several other reactions with Equation 9.²⁹ The correlation coefficients are presented in Table 2. The steric coefficients obtained are analyzed in terms of percent of steric effect by Equation 10, where m refers to a' , b' , or c' . These results are also presented in Table 2.

$$P_m = \frac{m}{\Sigma m} \times 100 \quad (10)$$

From the data in Table 2, one notices that the effect of the α -carbons is very dependent upon the reaction type. This dependence can be thought of as a measure of steric crowding in the transition state of these reactions. Charton maintains that "the steric effect of an alkyl group is dependent on the geometry of the transition state". Therefore, as more information is gathered on the dependence of $P_{a'}$, $P_{b'}$, and $P_{c'}$ with "known" transition state structures, one might expect that Equations 9 and 10 will become useful tools in determining "unknown" transition state structures.

Table 2

Set	P _a	P _b	P _c	r
1	59.5	19.7	20.8	0.956
2	92.2	7.8		0.981
3	88.4	8.9	2.7	0.974
4	44.3	55.7		0.937
5	41.9	35.8	22.3	0.962
6	74.7	20.3	5.0	0.959

Despite the success of Charton's approach to the separation of steric and polar effects, some workers feel that many of his data sets contain too few data points and therefore give deceptively high correlation coefficients.^{30,5} It is also argued that correlations should be used as tools and cannot be used in place of experiment. John Shorter has remarked concerning Charton's work,⁵ "One must not lose sight of the chemistry in a welter of statistics."

One must expect that correlation and prediction of reaction rates using Charton's approach may occasionally fail; however, this tool for probing chemical problems can also be expected to give enlightening results and is simply another step toward understanding the effects of structure on reactivity.

BIBLIOGRAPHY

1. (a) Brönsted and Pederson, *Z. Physik. Chem.*, 108, 185 (1924); (b) L. P. Hammett, *J. Am. Chem. Soc.*, 59, 96 (1937).
2. W. A. Sheppard, *Tetrahedron*, 27, 945 (1971).
3. L. S. Levitt and H. F. Widing, *Prog. Phys. Org. Chem.*, 12, 119 (1976).
4. R. W. Taft, Jr., "Steric Effects in Organic Chemistry", ed. M. S. Newman, Chapter 13, Wiley, New York, 1956.
5. N. B. Chapman and J. Shorter, "Advances in Linear Free Energy Relationships", Chapter 2, Plenum, New York, 1972.
6. C. K. Ingold, *J. Chem. Soc.*, 1032 (1930).
7. (a) M. L. Bender, *J. Am. Chem. Soc.*, 73, 1626 (1951); (b) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).
8. R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, 80, 2436 (1958).
9. D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958).
10. R. M. Noyes, *J. Am. Chem. Soc.*, 86, 971 (1964).
11. H. H. Jaffe, *Chem. Rev.*, 53, 191 (1953).
12. K. Okamoto, I. Nitta, T. Imoto, and H. Shingu, *Bull. Chem. Soc. Japan*, 40, 1905 (1967).
13. (a) C. D. Ritchie, *J. Phys. Chem.*, 65, 2091 (1961); (b) C. D. Ritchie and W. F. Sage, *Prog. Phys. Org. Chem.*, 2, 323 (1964); (c) W. Adcock and T. Khor, *J. Org. Chem.*, 43, 1272 (1978); (d) F. G. Bordwell and H. E. Fried, *Tetrahedron Lett.*, 1121 (1977).
14. (a) T. L. Brown, *J. Am. Chem. Soc.*, 81, 3229 (1959); (b) J. I. Brauman and L. K. Blair, *ibid.*, 92, 5986 (1970); (c) J. I. Brauman and L. K. Blair, *ibid.*, 91, 2126 (1969); (d) M. S. B. Munson, *ibid.*, 87, 2332 (1965).
15. M. Charton, *ibid.*, 91, 615 (1969).
16. M. Charton, *ibid.*, 97, 1552 (1975).

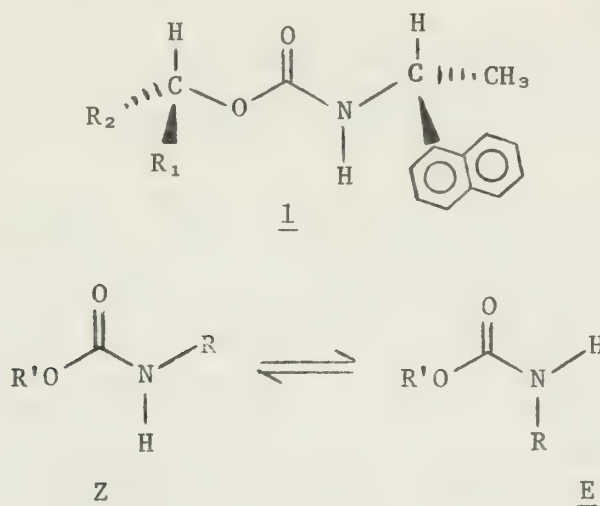
17. M. Charton, ibid., 97, 3691 (1975).
18. (a) M. Charton, J. Org. Chem., 41, 2906 (1976); (b) M. Charton, J. Am. Chem. Soc., 99, 5687 (1977); (c) M. Charton, J. Org. Chem., 44, 903 (1979).
19. M. Charton, ibid., 29, 1222 (1964).
20. M. Charton, ibid., 42, 3531 (1977).
21. M. Charton, ibid., 42, 3535 (1977).
22. M. Charton and B. Charton, J. Org. Chem., 43, 1161 (1978).
23. A. J. MacPhee and J. E. Dubois, Tetrahedron Lett., 2471 (1976).
24. M. D. Wunderlich, L. K. Leung, J. A. Sandberg, K. D. Meyer, and C. H. Yoder, J. Am. Chem. Soc., 100, 1500 (1978).
25. D. S. Kristol, R. C. Parker, and H. D. Perlmutter, J. Org. Chem., 41, 3205 (1976).
26. J. P. Idoux and J. O. Schreck, ibid., 43, 4002 (1978).
27. M. Charton, J. Am. Chem. Soc., 97, 6159 (1975).
28. M. Charton, J. Org. Chem., 42, 2528 (1977).
29. M. Charton, ibid., 43, 3995 (1978).
30. S. H. Unger and C. Hansch, Prog. Phys. Org. Chem., 12, 91 (1976).

DYNAMIC NMR STUDIES OF DIASTEREOMERIC CARBAMATES:
IMPLICATIONS TOWARD THE DETERMINATION OF RELATIVE
CONFIGURATION BY NMR AND LIQUID CHROMATOGRAPHY

Reported by Kirk Simmons

April 30, 1979

Diastereomeric carbamates similar to 1 are being used increasingly for the chromatographic resolution of racemic secondary alcohols.¹⁻⁸ Complimenting the chromatographic separability of these carbamates is the ease of retrieval of the resolved alcohol and the ability to assign the configuration of the carbinyl carbon from NMR spectral differences between the diastereomers.⁹ These spectral differences arise from the preferential population of the Z rotamer, the conformational rigidity of the carbamate backbone, and the resultant stereochemically dependent shielding by the α -naphthyl substituent.



We have previously reported that the diastereomers of type 1 carbamates have differing NMR spectral properties, depending on the configuration at the carbinyl center.⁹ On additional study we have found that some type 1 carbamates also exhibit NMR line broadening owing to a hindered rotational process about the carbonyl carbon-nitrogen bond. Since this NMR line broadening can complicate the mechanics of configurational assignments, we felt it necessary to further refine our earlier correlations of NMR spectral differences and chromatographic elution orders.⁹

Although NMR spectral differences exist between a pair of diastereomers, conformationally the diastereomers are very similar. This conformational behavior is essentially independent of the structure of the alcohol in the carbamate and is not influenced greatly by solvent polarity.

These findings are reassuring with respect to our earlier correlations of NMR spectral properties and chromatographic behavior and also demonstrate that even more information can be obtained by correlating the spectral properties of the diastereomers in the stopped exchange region.

BIBLIOGRAPHY

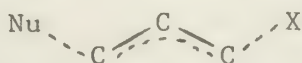
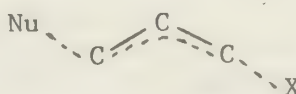
1. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, G. Keck, B. Goplan, S. Larsen, P. Siref, and J. Gras, J. Am. Chem. Soc., 100, 8034 (1978).
2. G. Schmid, T. Fukuyama, K. Alasaka, and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979).
3. T. Fukuyama, C. Wang, and Y. Kishi, J. Am. Chem. Soc., 101, 260 (1979).
4. T. Fukuyama, K. Alasaka, D. Karanewsky, C. Wang, G. Schmid, and Y. Kishi, J. Am. Chem. Soc., 101, 262 (1979).
5. W. H. Pirkle and P. E. Adams, J. Org. Chem., 43, 378 (1978).
6. W. H. Pirkle and C. W. Boeder, ibid., 43, 2091 (1978).
7. W. H. Pirkle and P. L. Rinaldi, ibid., 43, 2091 (1978).
8. W. H. Pirkle and P. L. Rinaldi, ibid., 44, 3083 (1979).
9. W. H. Pirkle and J. R. Hauske, ibid., 42, 1839 (1977).

SYN/ANTI STEREOSELECTIVITY IN S_N2' -LIKE REACTIONS

Reported by Paul Sherwin

May 3, 1979

The question of the syn/anti stereoselectivity in S_N2' -like¹ reactions has inspired a number of studies into the factors controlling the relative energies of the syn and anti transition states (Figures 1 and 2). An understanding of these factors would help not only to establish the utility of S_N2' -like reactions in stereoselective synthesis,² but also to refine theoretical models of stereoselectivity in allylic displacements.

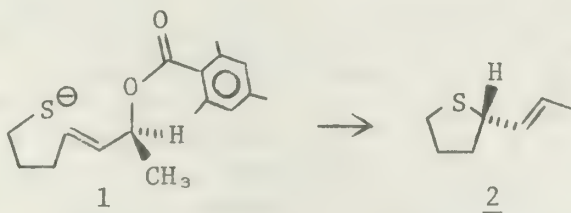
Figure 1: synFigure 2: anti

Molecular orbital studies lead to the conclusion that frontier orbital effects generally favor a syn transition state.^{3a,b} Electrostatic interactions are thought to favor syn attack with uncharged^{3b} and hydrogen-bonding nucleophiles^{3b,c} (the role of H-bonding has been questioned^{3d}), and anti attack with negatively charged nucleophiles.^{3b}

Experimental probes of S_N2' -like stereoselectivity employ stereochemical analysis of the products of S_N2' displacements on dissymmetric substrates. Studies of inter- and intramolecular S_N2' -like reactions in cyclic and acyclic systems have shown that both syn and anti products can form; the syn/anti ratio is a function of the nucleophile, the solvent, the leaving group, and counterions.

Syn attack was observed in the reactions of cyclohexenyl substrates with piperidine,^{4a-c} malonate anion,^{4a} and carboxylates;^{4d-f} of cis-dichloro-cyclobutene with methoxide ion;^{4g} of methallyl chlorides with amines;^{4h} of arene epoxides with organometallics,⁴ and in the cyclization of an allylic epoxide to form a prostaglandin precursor.^{4j}

Anti S_N2' -like attack was observed in the acetolysis of a 4-bromo-steroid^{5a} (alternative mechanisms may operate^{5b}); in the 1,6 conjugate additions of nucleophiles to arene oxides;⁴ⁱ in the cyclizations of linalyl p-nitrobenzoate to give α -terpineol,⁶ and of 1 to give 2;^{4b} in the biosynthesis of rosenonolactone;⁷ and in the reactions of cuprates with allylic and propargylic substrates.⁸



Mixtures of syn and anti products form with cyclohexenyl systems and mercaptides,^{4b} and with methallyl esters and amines.⁹ Hydride attack is syn or anti, depending on the substrate.^{8a} Chiral allenyl halides form stereoselectively syn or anti products, depending on conditions,¹⁰ although these reactions may be S_N1' examples.^{10b} Anchimeric assistance involving an intramolecular S_N2' -like attack may operate in the reactions of some

glycols,¹¹ cyclopentenyl dihalides,¹² codeine derivatives,¹³ and phenylthio cyclohexenyl esters.¹⁴

The dependence of the syn/anti product ratio on the substrate nature and reaction conditions indicates a need for a transition state model more detailed than the m.o. models. The effects of ion-pairing,¹⁵ hydrogen bonding in the transition state,^{3b-d} and conformational effects¹⁶ in S_N2' reactions have been discussed elsewhere. These approaches perhaps will provide the greatest understanding of the S_N2' stereoselectivity and pave the way to a successful predictive model.

BIBLIOGRAPHY

1. For reviews, see: F. G. Bordwell, *Acc. Chem. Res.*, 3, 281 (1970), and references cited therein.
2. See: D. Valentine and J. W. Scott, *Synthesis*, 329 (1978).
3. (a) W. Jefford and U. Burger, *Chimia*, 25, 297 (1971); (b) R. L. Yates, N. D. Epiotis, F. Bernardi, W. R. Cherry, and S. Shaik, *Top. Curr. Chem.*, 70, 126 (1977); (c) W. G. Young and I. J. Wilk, *J. Am. Chem. Soc.*, 79, 4793 (1957); (d) D. C. Dittmer and A. F. Marcantonio, *ibid.*, 86, 5621 (1964).
4. (a) G. Stork and W. N. White, *J. Am. Chem. Soc.*, 78, 4609 (1956); (b) G. Stork and A. F. Kreft, III, *ibid.*, 99, 3850, 3851 (1977); (c) A. A. Dobbie and K. H. Overton, *J. C. S. Chem. Commun.*, 722 (1977); (d) S. C. Welch, C. P. Hagan, D. H. White, W. P. Fleming, and J. W. Trotter, *J. Am. Chem. Soc.*, 99, 549 (1977); (e) L. Chiche, J. Caste, H. Cristol, and F. Plenat, *Tetrahedron Lett.*, 3251 (1978); (f) M. Ikota and B. Ganem, *J. Am. Chem. Soc.*, 100, 351 (1978); (g) W. Kirmse, F. Scheidt, and H. J. Vater, *ibid.*, 100, 3945 (1978); (h) R. M. Magid and O. S. Fruchey, *ibid.*, 99, 8368 (1977); 101, 2107 (1979); (i) A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccolo, and G. A. Berchtold, *ibid.*, 96, 6929 (1974) and references contained therein; (j) J. Martel, A. Blade-Font, C. Marie, M. Vivat, E. Toromanoff, and J. Buendia, *Bull. Soc. Chim. Fr.*, 131 (1978).
5. (a) J. Y. Satoh and T. T. Takahashi, *Chem. Commun.*, 1714 (1970); (b) R. B. Warneboldt and L. Weiler, *Tetrahedron Lett.*, 3413 (1971).
6. S. Godtfredsen, J. P. Obrecht, and D. Arigoni, *Chimia*, 31, 62 (1977).
7. D. E. Cane and P. P. N. Murthy, *J. Am. Chem. Soc.*, 99, 8329 (1977).
8. (a) See footnote 19 in reference 4h (1979); (b) P. Vermeer, H. Westmijze, H. Kleijn, and L. A. Van Dijk, *Recl. Trav. Chim. Pays-Bas*, 97, 56 (1978).
9. T. Oritani and K. H. Overton, *J. C. S. Chem. Commun.*, 454 (1978).
10. (a) O. J. Muscio, Y. M. Jun, and J. B. Philip, Jr., *Tetrahedron Lett.*, 2379 (1978); (b) S. R. Landor, B. Demetrious, R. J. Evans, R. Grzeskowiak, and P. Davey, *J. C. S. Perkin II*, 1995 (1972).
11. J. Cleophax, D. K. Duc, J. M. Dalaumeny, S. D. Gero, and A. Rolland, *J. C. S. Chem. Commun.*, 771 (1978).
12. A. C. Cope, L. L. Estes, J. R. Emery, and A. C. Haven, *J. Am. Chem. Soc.*, 73, 1199 (1951).
13. K. Abe, M. Onda, and S. Okuda, *J. C. S. Perkin I*, 316 (1973).
14. J. J. Uebel, R. F. Milaszewski, and R. E. Arlt, *J. Org. Chem.*, 42, 585 (1977).
15. (a) R. A. Sneen, *Acc. Chem. Res.*, 6, 46 (1973); (b) C. Georgoulis and G. Ville, *J. Chem. Res. (M)*, 3341 (1978).
16. E. Toromanoff, *Tetrahedron*, 34, 1665 (1978).

ANION-ASSISTED OXY-COPE REARRANGEMENTS

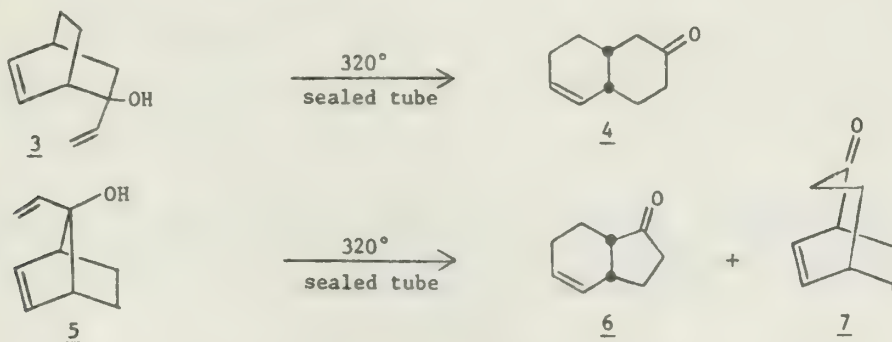
Reported by Clark Cummins

May 10, 1979

The use of pericyclic reactions has become one of the main synthetic tools available to the organic chemist, especially since the advent of a fundamental understanding of these processes in terms of orbital symmetry.¹ Next to the Diels-Alder reaction, probably the most useful of these types of reactions are the [3,3] sigmatropic rearrangements. The ability to effect complex molecular reorganization with a high degree of regio- and stereochemical control makes this type of process applicable to many organic studies. The prototype for these rearrangements is the Cope rearrangement of 1,5 hexadienes 1 \rightarrow 2 (X=H).^{2,3} This is thought to be a concerted process, though evidence exists for radicals or radicaloid species in certain cases.³ Substitution of a heteroatom for carbon at the 3-position of 1, and rearrangement of these systems has been widely investigated (Claisen,⁴ aza-Claisen,⁵ thia-Claisen⁶). Systems with more than one heteroatom have also been studied.⁷ Another interesting variation of the Cope process is the oxy-Cope rearrangement 1 \rightarrow 2 (X=OH). The end product, after tautomerization, is a δ,ϵ unsaturated aldehyde.

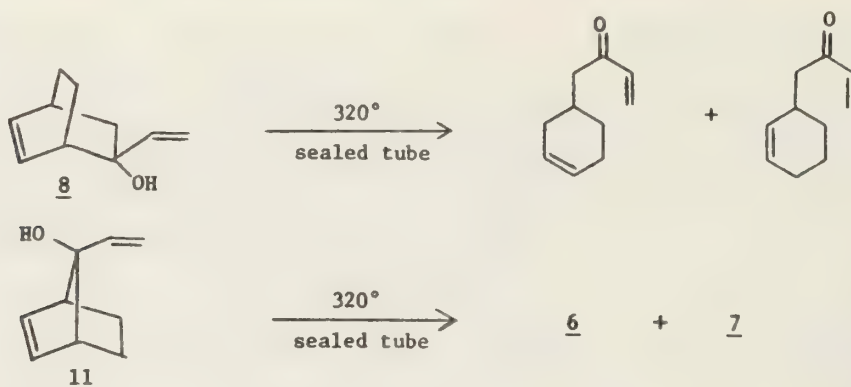


The term "oxy-Cope rearrangement" was first applied to the reaction observed in 1964 by Berson and Jones in the thermolysis of 2-endo-vinyl-2-exo-hydroxy-bicyclo[2.2.2]oct-5-enes (3) and syn-7-vinyl-anti-7-hydroxy norbornenes (5).⁸ Pyrolysis of 3 gave as the major product the oxy-Cope rearranged compound 4, while pyrolysis of 5 gave the oxy-Cope rearrangement product 6, and the product of [1,3] sigmatropic rearrangement 7, in a ratio of 1:14, respectively.

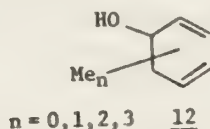


Pyrolysis of 2-exo-vinyl-2-endo-hydroxybicyclo[2.2.2]oct-5-ene (8) led to 9 and 10 as the major products. Incomplete pyrolysis of mixtures of 3 and 8 at three different temperatures led to recovery of starting material with no change in relative composition, indicating that the rates of rearrangement of 3 and 8 are virtually identical. Pyrolysis of anti-7-vinyl-syn-7-hydroxynorbornene (11) led to 6 and 7 (and other by-products) in a ratio of 1:19. Incomplete pyrolysis of mixtures of 5 and 11 at different temperatures again gave no change in relative composition of starting material, indicating identical rearrangement rates. These

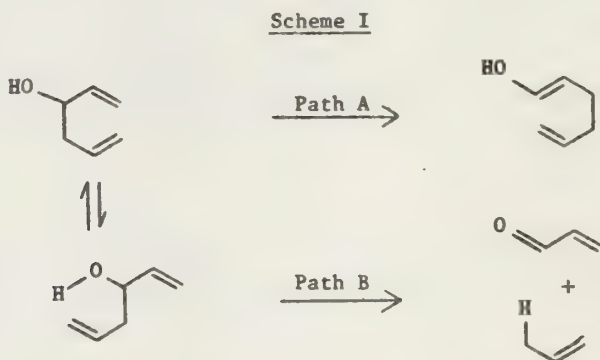
observations are incompatible with concerted rearrangement, but consistent with a diradical mechanism.



In 1967, Viola and co-workers studied the pyrolysis of mono-, di-, and tri- methyl substituted 3-hydroxy-1,5-hexadienes 12.⁹ In all cases



the products obtained could be explained by two different concerted rearrangement pathways, as illustrated for the parent unsubstituted compound in Scheme I. Path A shows the oxy-Cope rearrangement, while Path B shows the well-documented β -hydroxy olefin cleavage.¹⁰ Pyrolysis

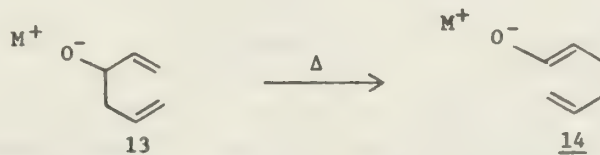


of the unsubstituted hydroxy diene 12 ($n = 0$) gave 60% rearrangement and 40% cleavage. Examination of the steric effects of methyl substitution in system 12 on the conformational equilibrium of the chair-like transition states preferred for pericyclic rearrangement¹¹ leads to a qualitative understanding of the relative ratios of oxy-Cope rearrangement and β -hydroxy olefin cleavage products in the various substituted cases. Radicals are mechanistically ruled out by the absence of cross-coupled products expected at the high temperatures used (320°-390°).

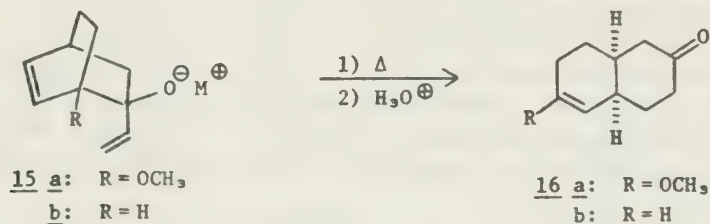
These seemingly inconsistent results can be reconciled if one examines the bicyclic compounds 3, 5, 8, and 11 more closely. Only 3 and 5 have the possibility of forming the cyclic transition state necessary for concerted rearrangement. In both cases they can only attain a boat-like conformation. Even though rearrangement through a boat-like transition state would normally be energetically more favorable than bond scission to a diradical

species,^{11,12} it has been shown¹³ that an α -oxy substituent lowers the activation energy for bond homolysis. In this case the energy decrease is apparently sufficient for the biradical mechanism to become the most favorable energetically. In general, though, unless complicating steric factors intervene (as in the above bicyclic case), the oxy-Cope is likely to proceed by a concerted process.

In 1975 Evans and Golob reported a study of the oxy-Cope rearrangement of 1,5 hexadiene alkoxides 13 \rightarrow 14.¹⁴ The models they chose for



this study were the [2.2.2] bicyclooctenes 15a and 15b, as kinetic data on the oxy-Cope rearrangement of the parent dienols was available.^{8a,15} Although the lithium and magnesium bromide alkoxides ($M = \text{Li}, \text{MgBr}$) showed



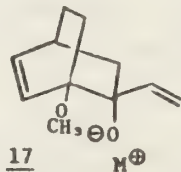
no signs of rearrangement after being heated at reflux in THF (66°) for 24 hours, the sodium alkoxide 15a ($M = \text{Na}$) rearranged to methoxy ketone 16a with a half life of 1.2 hr. The potassium alkoxide 15a ($M = \text{K}$) showed an incredible rate enhancement over dienol rearrangement, and gave methoxy ketone 16a in $\geq 98\%$ yield with a calculated half life of 1.4 min. This rate dependence on counterions suggested that further acceleration could be affected by the used of crown ethers. The rearrangement of 15a ($M = \text{K}$) in THF at 0° showed a limiting rate enhancement of 180 as varying amounts of 18-crown-6 were added, the value of 180 being reached with the addition of 3 equivalents. This same value of 180 was obtained in a study of the rearrangement of 15a ($M = \text{K}$) in HMPA. These data indicate that a maximal rate acceleration is obtained by ion-pair dissociation, and also indicate that rate dependence on solvent dielectric is minimal. First order rate constants determined at four temperatures gave the information listed in Table 1. This allows comparison of rate data between the alkoxide and parent alcohol. At 25°, the rearrangement of 15a ($M = \text{H}$) vs. 15a ($M = \text{K}$)

Table 1

Substrate	E_a , kcal/mole	Log A, kcal/mole	Temp. Range, °K
<u>13a</u> $M = \text{H}$	35.9 ± 1.8	12.6 ± 0.6	448-488
<u>13a</u> $M = \text{K}$	19.4 ± 0.7	10.3 ± 0.4	282-328
<u>13a</u> $M = \text{K}^*$	18.2 ± 0.1	11.5 ± 0.1	253-278
<u>13b</u> $M = \text{H}$	41.8 ± 0.4	12.5 ± 0.2	—

* 1.1 equivalents of 18-crown-6 added

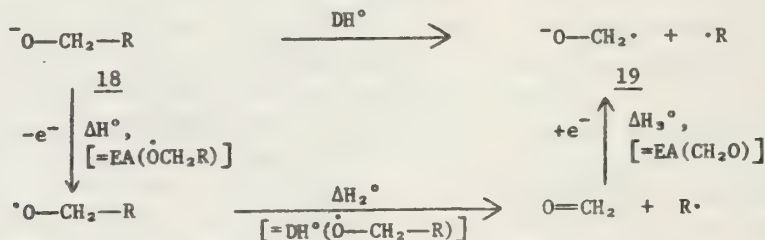
with the addition of 1.1 equivalents of 18-crown-6 shows a rate acceleration of 10^{12} . The rearrangement of 15b ($M=H$) vs. 15b ($M=K$) at 40° shows a rate acceleration of 10^{12} , and at 0° in the presence of crown ether an acceleration of 10^{17} . It is interesting to note that diene alkoxide 17 ($M=K$) shows no rearrangement after heating for 24 hr. This observation implies a concerted mechanism, though not excluding radical intermediates.



While there have been other reports in the literature of facile Cope rearrangements,¹⁶ and even alkoxide assisted Cope rearrangements,¹⁷ they were isolated examples, and did not receive much attention. This quantitative study by Evans, however, with its remarkable rate data, has stimulated a great deal of interest in this reaction. Specifically, the questions of the origin of the rate enhancement, the mechanism of the process, and its potential synthetic utility are raised.

In an effort to understand the nature of the alkoxide effect on the oxy-Cope rearrangement, Evans and Baillargeon studied the gas phase dissociation energy of the conversion 18 to 19.¹⁸ A simple Born-Haber cycle was established, as shown in Scheme II, and using experimentally determined

Scheme II



bond dissociation energies and electron affinities, the bond dissociation energies (DH°) of some alkoxides were calculated. The results are shown in Table 2. The data shows an impressive ΔD , the dissociation energy

Table 2

Substrate	$\text{DH}^\circ(\text{HO}-\text{CH}_2-\text{R})$, kcal/mole	$\text{DH}^\circ(\text{O}-\text{CH}_2-\text{R})$, kcal/mole	ΔD , kcal/mole
<u>18</u> , $\text{R} = \text{H}$	93	76	17
<u>18</u> $\text{R} = \text{CH}_3$	83	68	15
<u>18</u> $\text{R} = \text{CH}_2-\text{CH}=\text{CH}_2$	71	58	13

difference between the alcohol and alkoxide, of 13-17 kcal/mole. This is attributed to differential stabilization of the radical by overlap with the orbitals of the oxygen species. Calculations indicate that this overlap is more effective for the radical alkoxide than for the radical alcohol.¹⁹ The effects of various counterions are unknown, though predictions are that the charge-localized alkoxide will experience greater stabilization than the charge-delocalized ketyl. Thus, one might predict that if the oxy-Cope rearrangement proceeds through a transition state resembling a ketyl-like species, then decreasing the electronegativity

of the metal counterion (K instead of Na or Li) and increasing the cation solvating ability of the medium (crown ethers) should decrease the net stabilization of the ground state relative to the transition state due to the counterions, and increase the rate. The predictions are born out in the experimental results, but this does not necessarily prove the preceding ex-post facto argument, since no quantitative estimates of counterion effects on alkoxide homolysis are available.

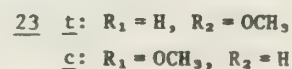
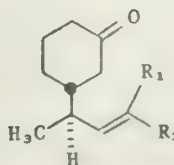
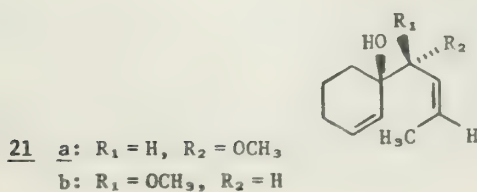
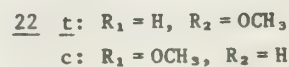
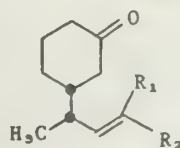
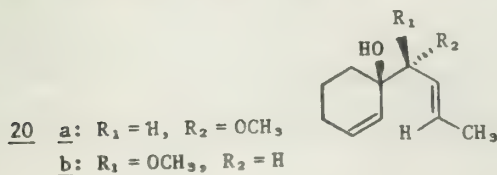
Ab-initio theoretical calculations of alcohol and alkoxide homolysis agree with the thermochemical results, and these are shown in Table 3. The comparison of the theoretical bond association energy difference relative to methanol of the alkoxide, with a value of 16.5 kcal/mole, to the corresponding thermochemical value, 17 kcal/mole, shows the close correlation. These calculations indicate a counterion effect qualitative in agreement with the earlier prediction, but in this case based on weakening the C-H bond by increasing delocalization of charge from the oxygen to the carbon.

Table 3

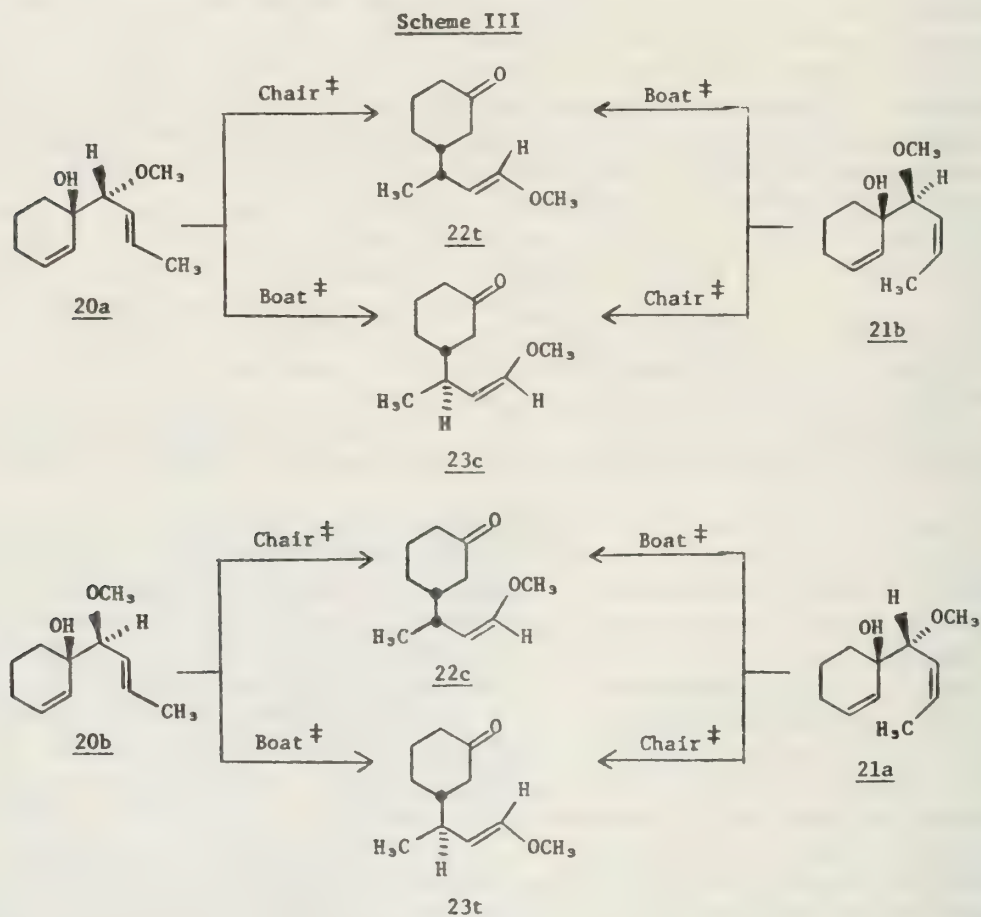
Substrate	Bond Energy, kcal/mole	ΔD (Relative to MeOH), kcal/mole
H ₃ CONa	80.6	10.1
H ₃ COK	79.0	11.7
H ₃ CO [⊖]	74.2	16.5

Thus, it is clear that the alkoxide has a weakening effect on the adjacent carbon-carbon bond, and can accelerate bond homolysis by destabilization of the ground state. However, the thermochemical and theoretical calculations yield an energy value which cannot account for the observed rate enhancement.²⁰ It thus appears unlikely that a radical mechanism is involved. This is supported by other work of Evans and Baillargeon in which thermochemical estimates of activation energies have ruled out a radical or ionic mechanism.²⁰ Apparently, the rate enhancement is due not only to ground state destabilization, but also to transition state stabilization, perhaps due to developing formation of the product enolate.

While the effect of the alkoxide on the rate of the oxy-Cope process was now better understood, the mechanism of the accelerated reaction was not. In order to determine whether or not the reaction was concerted, Evans and Nelson undertook a stereochemical study.²¹ They chose to study the anion-accelerated oxy-Cope rearrangements of the two pairs of diastereomeric dienols, 20a, 20b and 21a, 21b, to the ketones 22t, 22c and 23t, 23c.



Although at the onset of the work complete stereochemical assignments had not been made on the pairs of dienols, the reasoning was made that if all of the dienols underwent concerted rearrangement only, then from each dienol only two possible products could result. One would be formed via the chair transition state and one via the boat transition state, the amounts indicating the relative energies of the two transition states. This pattern is illustrated in Scheme III. If any one dienol gave more than 2 ketone products, or a product not derivable by either a chair or boat transition state, this would be definitive proof of a non-concerted rearrangement pathway.



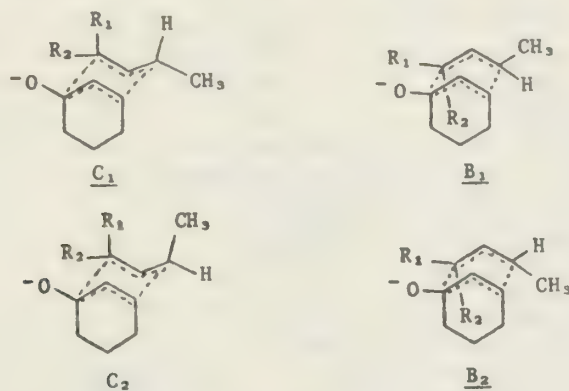
The dienols were rearranged using potassium hydride in diglyme at 110° for 38 hr. Products were separated by column chromatography and gas chromatography. The results of this study are shown in Table 4. The

Table 4

Dienol	Product Composition, %			
	22t	23c	22c	23t
<u>20a</u>	96	4	<1	<1
<u>20b</u>	<1	<1	77	28
<u>21a</u>	<1	0-2	2-0	98
<u>21b</u>	30	70	<1	<1

data very strongly suggest a concerted pathway for the rearrangement, showing essentially complete transfer of chirality and olefin geometric control. The difference in the ratio of cis:trans olefin geometry in the

rearrangement of 20a to 20b, as well as 21a to 21b, can be understood by examining the transition states. Structures C₁ and B₁ are the chair and boat transition states, respectively, for compounds 20a and 20b. In both cases, the chair transition state is conformationally more stable. For



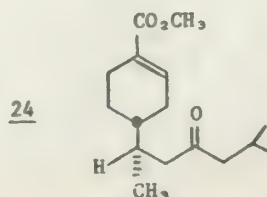
20a, R₁ = H, whereas for 20b, R₁ = OCH₃, and thus C₁ for 20b is less stable than C₁ for 20a, due to the pseudo-axial methoxy substituent, and $\Delta\Delta G^\ddagger$, the free energy difference between the chair and boat transition states, is smaller for 20b than 20a. Therefore, 20b shows less preference for the chair transition state than does 20a, and the cis-trans product ratios for the rearrangements of 20a and 20b reflect this. Structures C₂ and B₂ are the chair and boat transition states, respectively, for 21a and 21b. The same analysis predicts a larger preference for the chair transition state by 21a than 21b and also consistent geometric ratios.

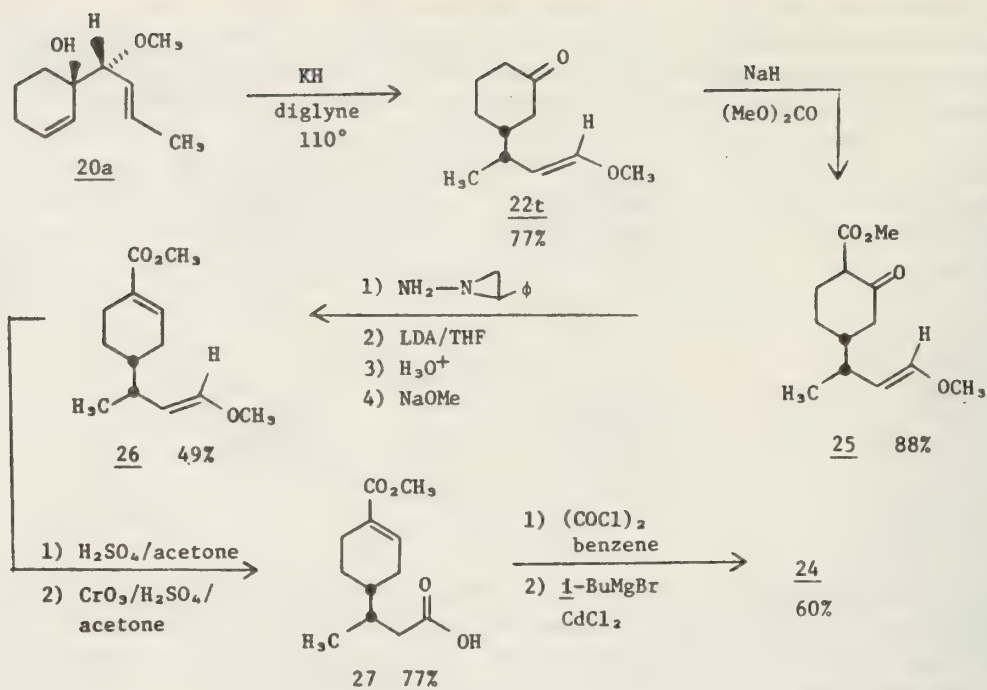
This study shows that the anion-assisted oxy-Cope rearrangement has all of the stereochemical requirements of a pericyclic reaction, and this strongly suggests that the mechanism is a concerted one. It therefore seems that, although the rate of the oxy-Cope rearrangement is enhanced by a factor of 10¹²-10¹⁷ by use of the alkoxide, the mechanism remains unchanged.

The [1,3] sigmatropic rearrangement of potassium alkoxides has also been reported,²² and rate enhancements of 10¹⁵-10¹⁷ are observed. Whether this also is a concerted process remains in question, however, as a comprehensive mechanistic study of these rearrangements has not been published.

As with all pericyclic processes, the capacity for the oxy-Cope rearrangement to afford products of controlled stereochemistry has made it a very attractive tool for the synthetic chemist. The utility of this reaction has been hampered by the high temperatures necessary, and the accompanying side reactions, such as β -hydroxy olefin cleavage. The advent of the alkoxide promoted rearrangement has allowed the use of this process in solution at room temperature and, except in the case of highly sterically congested systems, leads to much better rearrangement yields.⁹ This has resulted in its use in a number of natural product syntheses.

Evans and Nelson have reported a synthesis of (+)-erythro-juvabione (24),²¹ which depends on an anion-assisted oxy-Cope rearrangement to establish its stereochemistry. The synthetic pathway is outlined in the conversion of 20a to 24.





The key step is the rearrangement of **20a** to **22t**, establishing both contiguous stereochemical centers. Carbomethoxylation, Bamford-Stevens reduction and isomerization affords the α,β -unsaturated ester **26**. Hydrolysis of the enol ether, oxidation to the carboxylic acid, conversion to the acid chloride, and reaction with diisobutyl cadmium yields (\pm)-erythro-juvabione **24** in a stereochemically controlled fashion.

The accelerated oxy-Cope process has also found use in the synthesis of germacrene sesquiterpenes,²³ steroids,²⁵ perhydrozulenenes,²⁶ preparation of 1,6 dicarbonyl compounds,²⁷ quinone isoprenylation reactions,²⁸ and other endeavors.²⁹ In addition to providing potential synthetic routes to previously hard-to-obtain molecules, it has also yielded valuable mechanistic information which may be a key in understanding other complex molecular rearrangements.

BIBLIOGRAPHY

1. (a) R. B. Woodward and R. Hoffman, *J. Am. Chem. Soc.*, **87**, 395 (1965); (b) R. B. Woodward and R. Hoffman, *ibid.*, **87**, 2511 (1965).
2. S. J. Rhoads and N. R. Raulins, "Organic Reactions", Vol. 22, John Wiley and Sons, Inc., New York, 1975, pp. 1-252.
3. R. Wehrli, D. Bellus, H. Hansen, and H. Schmid, *Chimia*, **30**, 416 (1976).
4. L. Claisen, *Ber. Dtsch. Chem. Ges.*, **45**, 3157 (1912).
5. B. S. Thayagarajan, "Advances in Heterocycles", A. Katritzky, ed., Academic Press, New York, 1967, Vol. 8, p. 143.
6. (a) H. Kwart and T. J. George, *J. Chem. Soc. Chem. Commun.*, 433 (1970); (b) K. Kondo and O. Ojima, *ibid.*, 62 (1972).
7. R. M. Coates and I. M. Said, *J. Am. Chem. Soc.*, **99**, 2355 (1977).
8. (a) J. Berson and M. Jones, *ibid.*, **86**, 5017 (1964); (b) J. Berson and M. Jones, *ibid.*, **86**, 5019 (1964).
9. A. Viola, E. James Iorio, Katherine K. Chen, George M. Glover, Ulhas Nayak, and Phillip J. Kacinski, *ibid.*, **89**, 3462 (1967).

10. (a) R. T. Arnold and G. Smolinsky, *ibid.*, 81, 6443 (1959); (b) R. T. Arnold and G. Smolinsky, *J. Org. Chem.*, 25, 129 (1960); (c) G. G. Smith and R. Taylor, *Chem. Ind. (London)*, 949 (1961); (d) G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965).
11. W. v. E. Doering and W. R. Roth, *Tetrahedron*, 18, 67 (1962).
12. (a) R. B. Woodward and T. J. Katz, *Tetrahedron*, 5, 70 (1954); (b) R. C. Cookson, N. S. Isaacs, and M. Szelke, *ibid.*, 20, 717 (1964); (c) G. S. Hammond and R. D. Boer, *J. Am. Chem. Soc.*, 86, 899 (1964); (d) D. J. Trecker and J. P. Henry, *ibid.*, 86, 902 (1964).
13. (a) E. G. Foster, A. C. Cope, and F. Daniels, *J. Am. Chem. Soc.*, 69, 1893 (1947); (b) G. R. Aldridge and G. W. Murphy, *ibid.*, 77, 11 (1951).
14. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 97, 4765 (1975).
15. D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 137 (1972).
16. (a) P. Yates and P. Eaton, *Tetrahedron Lett.*, 11, 5 (1960); (b) R. C. Cookson, J. Hudec, and R. O. Williams, *ibid.*, 22, 29 (1960); (c) R. Breslow and J. M. Hoffman, Jr., *J. Am. Chem. Soc.*, 94, 2111 (1972).
17. (a) S. Swaminathan, J. P. John, and S. Ramachandran, *Tetrahedron Lett.*, 729 (1962); (b) S. Swaminathan, K. G. Srinivasan, and P. S. Venkataramani, *Tetrahedron*, 26, 1458 (1970).
18. (a) D. A. Evans and D. J. Baillargeon, *Tetrahedron Lett.*, 3315 (1978); (b) D. A. Evans and D. J. Baillargeon, *ibid.*, 3319 (1978).
19. M. L. Steigerwald, W. A. Goddard, III, and D. A. Evans, *J. Am. Chem. Soc.*, 101, 1994 (1979).
20. D. J. Baillargeon, Ph.D. Thesis, California Institute of Technology, 1974.
21. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.*, in press.
22. (a) R. W. Thies and E. P. Seitz, *J. Chem. Soc. Chem. Commun.*, 846 (1976); (b) S. R. Wilson, D. T. Mao, K. M. Jernberg, and S. T. Ezmirly, *Tetrahedron Lett.*, 2559 (1977); (c) S. R. Wilson and D. T. Mao, *J. Chem. Soc. Chem. Commun.*, 479 (1978); (d) R. W. Thies and E. P. Seitz, *J. Org. Chem.*, 43, 1050 (1978).
23. W. C. Still, *J. Am. Chem. Soc.*, 99, 4186 (1977).
24. W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, 34, 3587 (1969).
25. M. E. Jung and J. P. Hudspeth, *J. Am. Chem. Soc.*, 100, 4309 (1978).
26. H. O. House, T. S. B. Sayer, and C. Yau, *J. Org. Chem.*, 43, 2153 (1978).
27. (a) D. Seebach, K. Geiss, and M. Pohrakotr, *Angew. Chem. Int. Ed. Eng.*, 15, 437 (1976); (b) D. A. Evans, D. J. Baillargeon, and J. V. Nelson, *J. Am. Chem. Soc.*, 100, 2242 (1978).
28. D. A. Evans and J. M. Hoffman, *J. Am. Chem. Soc.*, 98, 1983 (1976).
29. (a) L. S. Hegedus and B. R. Evans, *J. Am. Chem. Soc.*, 100, 3461 (1978); (b) T. Miyashi, A. Hazato, and T. Mukai, *ibid.*, 100, 1008 (1978); (c) G. A. Kraus and K. Frazier, *Synthetic Comm.*, 8, 483 (1978); (d) D. Gange and P. Magnus, *J. Am. Chem. Soc.*, 100, 7746 (1978).

ASYMMETRIC SYNTHESIS: CARBON-CARBON BOND FORMATION VIA ENAMINES, OXAZOLINES, AND RELATED COMPOUNDS

Reported by Peter Becker

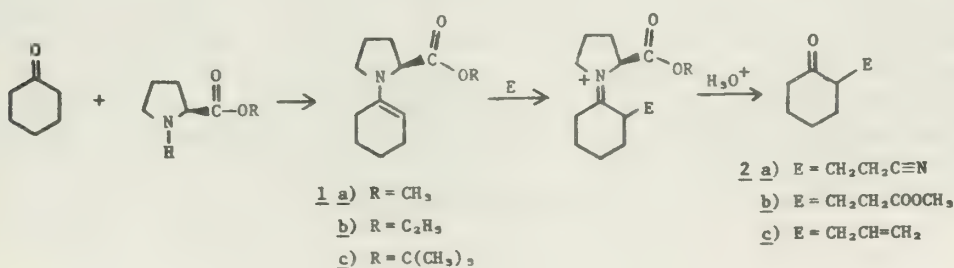
April 16, 1979

Control of the chirality of a developing asymmetric center during carbon-carbon bond formation has proven to be a major challenge. Addition of organometallic compounds to a carbonyl group, conjugate addition to α,β -unsaturated compounds, and cycloaddition were the main methods cited in the review by Morrison and Mosher of work before 1969.¹ While it is difficult to generalize, the reactions often gave optical yields of less than 40%, and these procedures did not facilitate formation of a chiral center adjacent to a carbonyl group.

Since 1969 good progress has been made in the field of asymmetric synthesis which has been reviewed by Valentine and Scott^{2,3} and in 1977 by Kagan and Fiaud.⁴ Some of the most successful asymmetric syntheses involving carbon-carbon bond formation have been accomplished using enamines, metaloenamines, oxazolines, and hydrazones. These reactions develop a chiral center adjacent to the functionalized carbon. Since these classes of compounds are carbonyl equivalents, they could be valuable for use in additional synthetic steps.

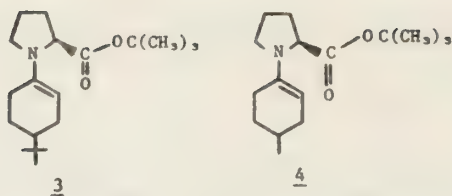
Enamines. In 1962 Stork and co-workers reported that enamines derived from secondary amines and ketones or aldehydes had been alkylated or acylated.⁵ If a chiral amine is used to form the enamine, asymmetric induction might be expected. Yamada and co-workers have made use of secondary amines derived from L-proline. Scheme I shows the alkylation of cyclohexenamines, which proceeded in variable yield.⁶

Scheme I

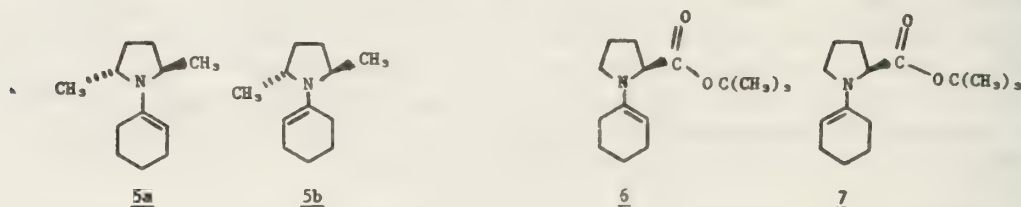


Using acrylonitrile, methyl acrylate, and allyl bromide as the electrophile (E) gave products 2 a, b, and c, respectively in moderate yield, but addition products of alkyl iodides were reported in much lower yield. Optical yields were reported as high as 59% enantiomeric excess (e.e.) in product 2b using enamine 1c; however, the chemical yield was only 17%. Generally optical yields were much lower using 1a and 1b. The problem in this reaction is that the higher temperatures and polar solvents required to achieve acceptable chemical yield drastically decrease the optical yield.

Yamada also reported alkylation of 4-substituted cyclohexanone via enamines 3 and 4.⁷ Although chemical yields were low, he found a high ratio of trans (83%) to cis (17%) products when using acrylonitrile and allyl bromide as the electrophiles.



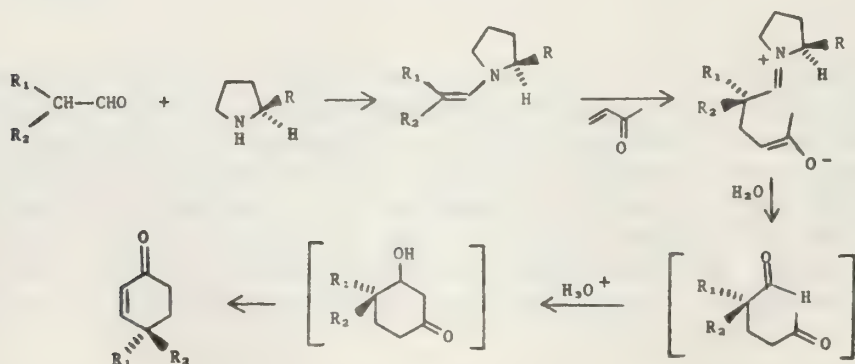
More recently Whitesell reported successful asymmetric alkylation of cyclohexanone using trans-2,5-dimethylpyrrolidine.⁸ Since this amine has a C-2 axis of symmetry, the two conformers 5a and 5b are identical. This has the advantage that a methyl group always blocks one side of the enamine. With enamines derived from proline, the rotation about the C-N bond from 6 to 7 removes the blocking group from the site of reaction. Approach from either side of conformer 7 may be expected to lead to transition states of about the same energy, so selectivity may be low.



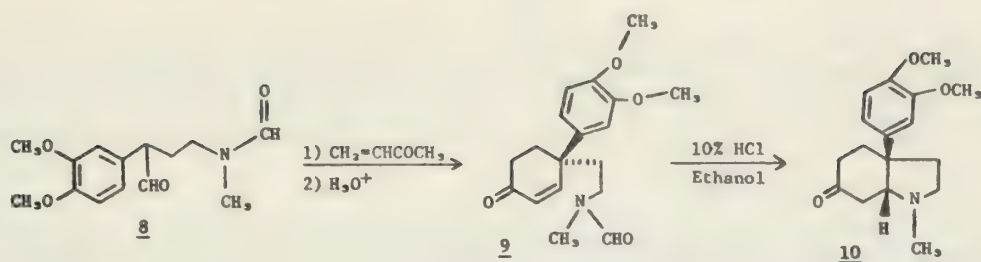
On alkylation of 5 with methyl iodide, n-propyl iodide, and allyl bromide, products were found to possess 83, 93, and 82% e.e., respectively, as determined by optical rotation. Chemical yield (50-80%) was also improved over Yamada's method.

Asymmetric synthesis of 4,4-disubstituted-2-cyclohexenones via enamines has been reported by Yamada.⁹ Observed optical rotation, not optical yield, was usually reported. A study of proline derivatives showed 2-(3-pyridylmethyl)-pyrrolidine produced the highest optical yield, 54% e.e.^{9c} Scheme II shows the reaction sequence leading to the cyclohexenones. It is important to note that R₁ or R₂ must be phenyl to produce acceptable chemical and optical yields.

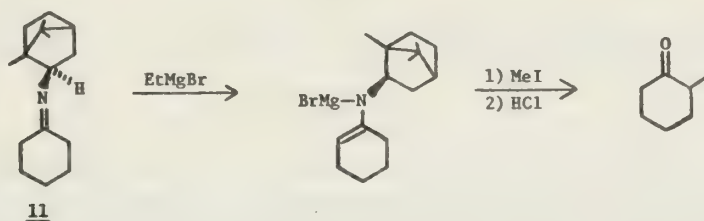
Scheme II



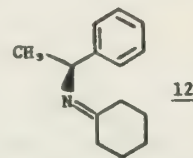
This sequence has been applied to the synthesis of (+)-Mesembrine (10).^{9d} Formation of the enamine of aldehyde 8 with L-proline pyrrolidide followed by addition of methyl vinyl ketone and hydrolysis in acetic acid/water solution gives the cyclohexenone 9 in 38% yield. Further treatment with 10% HCl in ethanol gave mesembrine (29% e.e.).



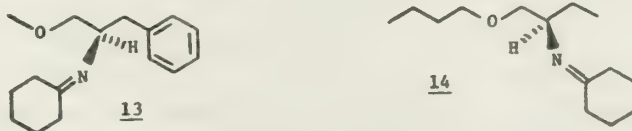
Metaloenamines. The use of metalated imines, first reported by Stork and Dowd¹⁰ has improved both optical and chemical yields of alkylations as compared to the enamine reaction. The first report of asymmetric synthesis using a metaloenamine was made by Horeau in 1968.¹¹ The isobornylimine of cyclohexanone 11 was metalated with ethylmagnesium bromide. Alkylation with methyl iodide followed by hydrolysis with hydrochloric acid gave 2-methylcyclohexanone in 72% e.e. Other alkylating agents gave lower optical yields.



Yamada reported use of optically active (S)- α -phenethyl amine and *sec*-butyl amine for asymmetric induction.¹² Metalation with lithium diisopropylamide (LDA) followed by alkylation gave poor results using *sec*-butylamine, e.g. 6% e.e. Moderate results, 26-37% e.e., were achieved with α -phenethylamine using a variety of alkylating agents.

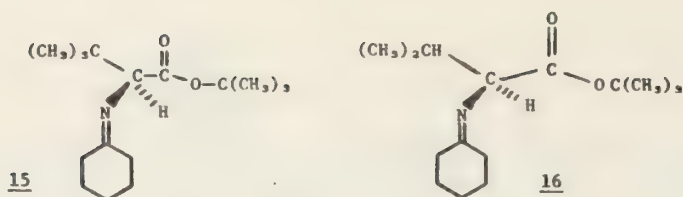


In 1976 Meyers reported an improvement on this type of synthesis.¹³ Using a chiral methoxyamine derived from *R*-phenylamine to form the cyclohexylimine 13, it was found that metalation with LDA at -20°C followed by alkylation at -78°C gave 2-alkylcyclohexanones in 50 to 80% chemical yield with 82 to >92% e.e.



Similarly, Whitesell used a chiral amine to form the cyclohexylimine 14 which could be metalated with isopropyl magnesium bromide and alkylated with methyl iodide at -78°C .¹⁴ After hydrolysis, (R)-2-methylcyclohexanone was obtained in 81% e.e.

A variation of this method for alkylation of cyclohexanones was recently reported by Koga.¹⁵ The *t*-butyl esters of (L)-*t*-Lucine and (L)-valine were used to form imines 15 and 16. Using LDA to form the lithio enamine, followed by alkylation with dimethylsulfate, 2-methylcyclohexanone was formed in 98% e.e. Additional examples with methyl iodide, *n*-propyl iodide and allyl bromide gave products in 84-97% e.e.

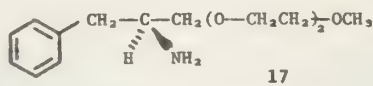


Alkylation of cyclohexanone by the procedures described is summarized in Table 1. Formation of 2,2-disubstituted cyclohexanones was also reported to proceed with high enantio selectivity (94-96% e.e.) when the initial substituent was a phenyl group.

Table 1. Asymmetric Alkylations of Cyclohexanone

Enamine or Imine	Base	Electrophile	% Yield	% e.e.	Ref.
<u>1c</u>	None	$\text{CH}_2=\text{CHCO}_2\text{CH}_3$	22	53	6
<u>1c</u>	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	20	30	6
<u>5</u>	"	CH_3I	—	83	8
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	—	82	8
<u>11</u>	$\text{C}_2\text{H}_5\text{MgBr}$	CH_3I	58	72	11
<u>12</u>	LDA	"	42	26	12
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	51	33	12
"	"	$n\text{-C}_3\text{H}_7\text{I}$	48	37	12
<u>13</u>	"	$(\text{CH}_3)_2\text{SO}_4$	72	82	13
"	"	$n\text{-C}_3\text{H}_7\text{I}$	50	>95	13
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	80	>90	13
<u>14</u>	$(\text{CH}_3)_2\text{CHMgBr}$	CH_3I	~ 58	85	14
<u>15</u>	LDA	$(\text{CH}_3)_2\text{SO}_4$	65	98	15
"	"	$\text{CH}_2=\text{CHCH}_2\text{Br}$	75	84	15
"	"	$n\text{-C}_3\text{H}_7\text{I}$	70	97	15
<u>16</u>	"	$(\text{CH}_3)_2\text{SO}_4$	59	84	15

Meyers and co-workers have extended the use of chiral lithio enamines to acyclic ketones¹⁶ and aldehydes. The effects of varying the base and the substituents on the chiral amine were tested in the synthesis of 2-methyloctanal.¹⁷ Using amine 17 to form the imine followed by metalation with lithium 2,2,6,6-tetramethylpiperidide and alkylation with methyl iodide gave the optimum optical yield (58%) of (S)-2-methyloctanal.



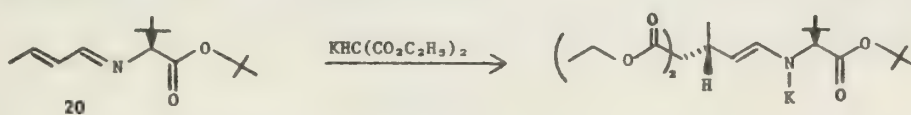
Asymmetric alkylation of ketimines proved to be more difficult under the same conditions. Kinetic control of initial proton attraction forms a mixture of the Z and E isomers 18 and 19. Alkylation at this point gives



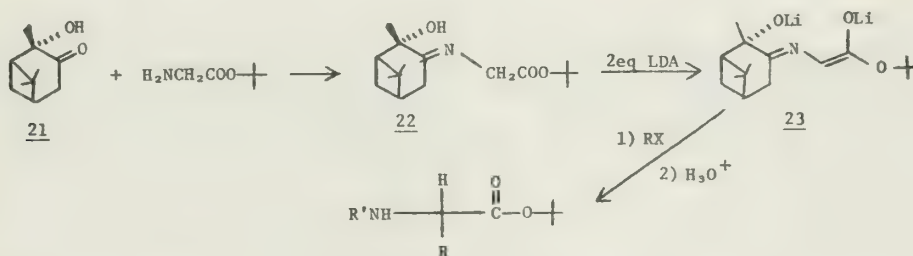
poor optical yields. Heating the lithioenamine in THF at reflux followed by cooling to -78°C allows thermodynamic control. The E isomer 19 is favored when R_2 is smaller than the amine group (Li-N-R_3), e.g. straight

chain alkyl, and optical yields of 76 to 98% e.e. are found. When R_2 is comparable in size to the amine group, e.g. benzyl or phenyl, there is little preference for 18 or 19, so low optical yields are found. Perhaps this method of equilibration would improve optical yields in the alkylation of aldehydes.

To this point all reactions described have had the asymmetric center being formed adjacent to the carbonyl. Yamada and Koga have reported formation of the chiral center at the β carbon using α,β -unsaturated aldimines.^{18,19} The *t*-butyl ester of *t*-leucine consistently provided the highest optical yields. Addition of diethyl potassium malonate to imine 20 gave 48% product in 86% e.e. Addition of a variety of Grignard reagents to 20 gave products in about 50% yield and greater than 90% e.e. It was suggested that the high enantioselectivity may be due to complexation of the organometallic with the carbonyl oxygen and the nitrogen. Attack at the β position from the side opposite the *t*-butyl group will give the products found.



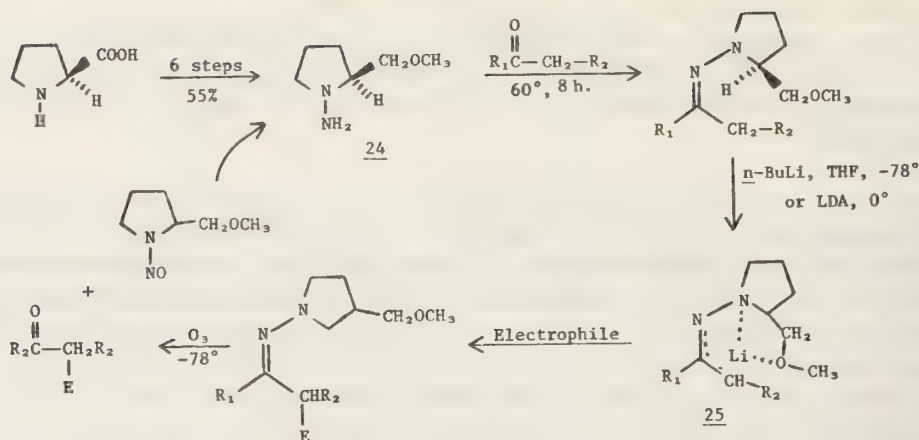
A final use of imines reverses the role of the carbonyl compound and the amine. Chiral ketone 21 and symmetric *O*-*t*-butylglycine formed imine 22 as reported by Yamada.²⁰ Treatment with 2 equivalents of LDA gives intermediate 23 which on alkylation and hydrolysis gives optically active amino acids in 66 to 83% e.e. This appears to be a reasonable route to optically active amino acids.



<u>RX</u>	<u>Yield</u>	<u>Optical Yield</u>
MeI	52%	83%
<i>i</i> -BuI	50%	83%
PhCH ₂ Br	79%	72%
3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂ Br	62%	66%

Hydrazones. Similar to enamines, chiral hydrazones have been used as the chiral auxiliary for asymmetric synthesis. Corey and Enders have shown that metalated hydrazones can function as enolate equivalents.²¹ Enders and co-workers have used chiral hydrazine, 24, a derivative of *S*-proline, in the synthesis of asymmetric α -substituted ketones^{22,23} and aldehydes.^{23,24} Scheme II shows the synthetic sequence. In this sequence it can be seen that after cleavage and reduction of the nitrosamine, the original hydrazine 24 may be recovered and reused. Dye sensitized cleavage by singlet oxygen has also been reported.²⁵

Scheme II



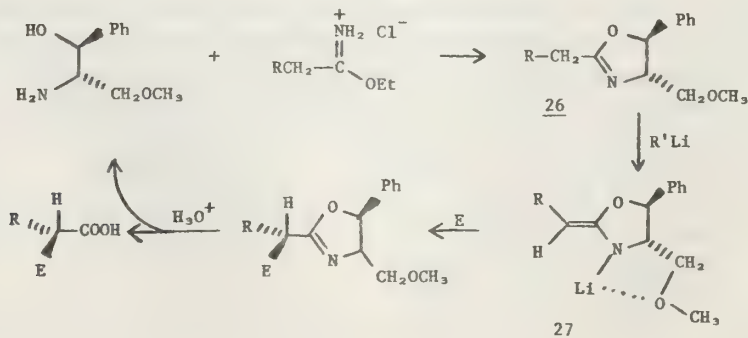
Results have been variable using this scheme for asymmetric induction as seen from the data in Table 2. The asymmetric induction in this example may be in part due to the complexation of the lithium ion with the ether oxygen and the ring nitrogen as shown in structure 25.

Table 2

Starting Compound	Electrophile	%e.e. (Conformation)	%Yield	Ref.
CH ₃ CH ₂ CHO	C ₆ H ₅ CH ₂ Br	82 (S)	62	24
CH ₃ (CH ₂) ₆ CHO	CH ₃ I	87 (R)	61	24
cyclohexanone	(CH ₃) ₂ SO ₄	85 (R)	70	22
cyclohexanone	CH ₃ CH ₂ CH ₂ I	87 (R)	73	22
acetone	CH ₃ (CH ₂) ₃ CHO	36	48	23
acetone	(CH ₃) ₂ CHCOCH ₃	47	58	23
(CH ₃) ₃ C COCH ₃	c-C ₆ H ₁₁ CHO	62	32	23

Oxazolines. The synthetic versatility of 2-oxazolines has been surveyed by Meyers and Mihelich.²⁶ Asymmetric synthesis using chiral oxazolines as intermediates has been developed rapidly in recent years by Meyers and co-workers. The work from 1974 to 1978 has been summarized by Meyers.²⁷ Scheme III outlines the general approach to the use of oxazolines in asymmetric synthesis. Synthesis of the chiral oxazoline 26 is easily achieved by the reaction of the appropriate amino alcohol and the ethyl imidate of the alkyl nitrile^{28,29} or an ortho carboxylic acid.²⁹ Treatment with base forms anion 27 which can then react with an electrophile. Hydrolysis with aqueous acid regenerates the optically active amino alcohol without racemization plus the asymmetric derivatized acid.

Scheme III

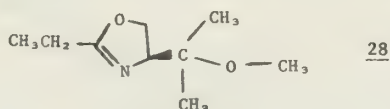


Alkylation followed by hydrolysis will give chiral carboxylic acids in good yield as seen in Table 3. Hansen reported the synthesis of (S)-2-

Table 3

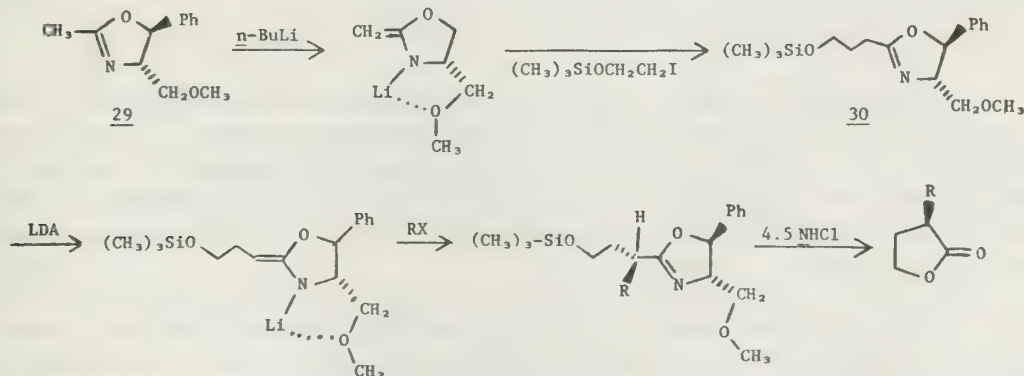
Oxazoline	Alkylating Agent	Temp.	%Yield Acid	%e.e. (Conf.)
1) <u>26</u> , R = CH ₃	C ₂ H ₅ I	-98	84	78 (S)
2) "	n-C ₃ H ₇ I	-98	79	72 (S)
3) "	n-C ₄ H ₉ I	-78	65	75 (S)
4) "	PhCH ₂ Cl	-78	62	74 (A)
5) <u>26</u> , R = PhCH ₂	(CH ₃) ₂ SO ₄	-98	75	78 (R)
6) <u>26</u> , R = H	(dl)-2-butylI	-65	-	34 (R)
7) "	(dl)-2-hexylI	-65	-	47 (R)
8) "	(dl)-3-octylI	-50	-	58 (R)
9) <u>28</u>	n-C ₆ H ₉ I	-98	88	75 (S)

methyl hexanoic acid in 75% e.e. using oxazoline 28.³⁰ Since this has the opposite configuration at carbon-4 from that of Meyers' oxazoline 26, one might have expected the opposite configuration in the product. This is in



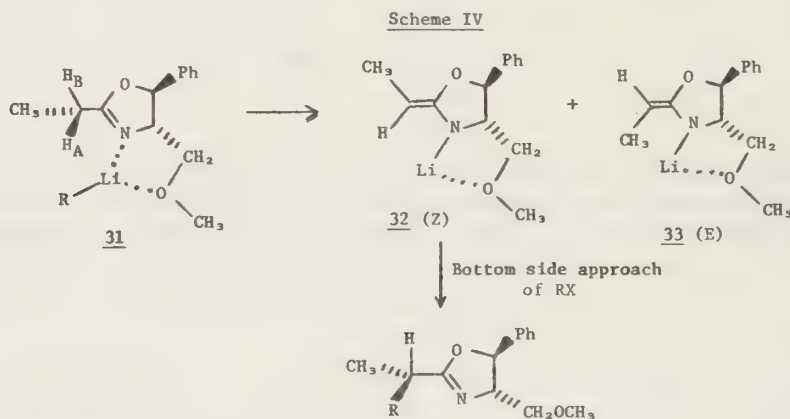
fact not the case. Use of secondary iodides to form chiral centers β to the carboxyl group has been reported.³¹ This is a kinetic resolution using an excess of racemic iodide. While perhaps not synthetically useful, this shows there is significant difference in the rates of the reactions for the two configurations of alkyl iodides.

Alkylation of oxazoline 29 with ethylene oxide followed by chlorotrimethylsilane or the equivalent, 2-trimethylsilyloxyethyl iodide, gives 30. Treatment with additional base, followed by alkylation and hydrolysis gives γ -butyrolactones in 64 to 73% e.e. and in chemical yields of 58 to 75%.³² Use of 3-trimethylsilyloxypropyl iodide similarly gives δ -valero lactones.



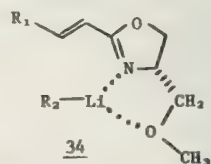
Similar to Yamada's and Koga's addition of Grignard reagents to α,β -unsaturated imines, organolithium reagents add to the β -position of α,β -unsaturated oxazolines.³³ This reaction gives products in variable yields (31 to 76%) but uniformly high optical purity (>90% e.e.). Attempts have also been made to generate chiral centers β to the oxazoline using an aldehyde as the electrophile but results have been poor (<25% e.e.).³⁴

Discerning the mechanism of these reactions and their high stereoselectivity is of interest in planning other asymmetric syntheses. The reaction proceeds in two distinct steps as shown in Scheme IV, both of which require stereoselectivity. The first step, proton abstraction, has been shown by ^{13}C NMR spectroscopy to give a 9:1 ratio of Z (32) to E (33) products.³⁵ Meyers has proposed that the lithium initially complexes with the methoxy oxygen and the ring nitrogen. Decrease in selectivity when the methoxymethyl group is replaced by methyl supports this proposition.³⁶ To relieve crowding the ethyl group is largely in the conformation shown in structure 31. Removal of H_A then gives the Z geometry.



The second step, alkylation, must also be selective. Meyers has shown that if the phenyl group is replaced with methyl or hydrogen, the selectivity falls greatly.³⁶ The opposite configuration yet high selectivity found using oxazoline 28 might suggest that the first step proceeds as described above. The dimethylmethoxymethyl group is sufficiently bulky to block bottom side approach of the alkylation agent just as the phenyl group blocks topside approach in oxazoline 31.

Addition to the β carbon by nucleophilic attack takes place in only one step and occurs in high optical yield even in the absence of the phenyl group.^{33a} This suggests a complex such as 34 may lead to the transition state.



Conclusion. These compounds, oxazolines, enamines, and related species provide useful means of asymmetric synthesis. They can be used to generate a chiral center while leaving the carbonyl function or equivalent intact. Another important consideration is the ease with which the chiral auxiliary can be recovered. This allows repeated use and is an economical factor, too.

From these studies it can be seen that steric factors remain important, but also that intramolecular complexation as a means of control is important. Since the metaloenamines and oxazolines that contain ether oxygens employ both factors, they appear at this time to be the most promising means for successful asymmetric syntheses of ketones, aldehydes, and carboxylic acids. Perhaps additional refinements of the procedures using these compounds will allow consistent results with optical yields greater than 90%.

BIBLIOGRAPHY

1. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971.
2. J. W. Scott and D. Valentine, Jr., *Science*, 184, 943 (1974).
3. D. Valentine, Jr., and J. W. Scott, *Synthesis*, 329 (1978).
4. H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 10, (1977).
5. G. Stork, A. Brizzolara, H. Landesman, J. Szmuzkovic, and R. Terrell, *J. Am. Chem. Soc.*, 85, 207 (1962).
6. (a) S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Lett.*, 4233 (1969); (b) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, 20, 246 (1972).
7. K. Hiroi and S. Yamada, *Chem. Pharm. Bull.*, 21, 47 (1973).
8. J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, 42, 1663 (1977).
9. (a) S. Yamada and G. Otani, *Tetrahedron Lett.*, 4237 (1969); (b) G. Otani and S. Yamada, *Chem. Pharm. Bull.*, 21, 2112 (1973); (c) T. Sone, K. Hiroi, and S. Yamada, *ibid.*, 21, 2331 (1973); (d) G. Otani and S. Yamada, *ibid.*, 21, 2130 (1973).
10. G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, 85, 2178 (1962).
11. D. Meá-Jacheet and A. C. Horeau, *Bull. Soc. Chim. Fr.*, 4571 (1968).
12. M. Kitamoto, K. Hiroi, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.*, 22, 459 (1974).
13. A. I. Meyers, D. R. Williams, and M. Druelinger, *J. Am. Chem. Soc.*, 98, 3032 (1976).
14. J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, 42, 377 (1977).
15. S. Hashimoto and K. Koga, *Tetrahedron Lett.*, 573 (1978).
16. A. I. Meyers and D. R. Williams, *J. Org. Chem.*, 43, 3245 (1978).
17. A. I. Meyers, G. S. Poindexter, and Z. Brich, *ibid.*, 43, 892 (1978).
18. S. Hashimoto, S. Yamada, and K. Koga, *J. Am. Chem. Soc.*, 98, 7450 (1976).
19. S. Hashimoto, N. Komeshima, S. Yamada, and K. Koga, *Tetrahedron Lett.*, 2907 (1977).
20. S. Yamada, T. Oguri, and T. Shori, *J. Chem. Soc., Chem. Commun.*, 136 (1976).
21. E. J. Corey and D. Enders, *Chem. Ber.*, 111, 1337, 1362 (1978).
22. D. Enders and H. Eichenauer, *Angew. Chem. Int. Ed. Eng.*, 15, 549 (1976).
23. H. Eichenauer, E. Friedrich, W. Lutz, and D. Enders, *Angew. Chem. Int. Ed. Eng.*, 17, 206 (1978).
24. D. Enders and H. Eichenauer, *Tetrahedron Lett.*, 191 (1977).
25. E. Friedrich, W. Lutz, H. Eichenauer, and D. Enders, *Synthesis*, 893 (1977).
26. A. I. Meyers and E. D. Mihelich, *Angew. Chem. Int. Ed. Eng.*, 15, 270 (1976).
27. A. I. Meyers, *Acct. Chem. Res.*, 11, 375 (1978).
28. A. W. Dox, *Org. Syn. collected Vol. 1*, p. 5 (1942).
29. (a) A. I. Meyers, G. Knaus, and K. Kamata, *J. Am. Chem. Soc.*, 96, 268 (1974); (b) A. I. Meyers and G. Knaus, *ibid.*, 96, 6508 (1974); (c) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *ibid.*, 98, 567 (1976).
30. J. F. Hansen and C. S. Cooper, *J. Org. Chem.*, 41, 3219 (1976).
31. (a) A. I. Meyers and K. Kamata, *J. Am. Chem. Soc.*, 98, 2290 (1976); (b) A. I. Meyers and K. Kamata, *J. Org. Chem.*, 39, 1603 (1974).
32. A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, 40, 1186 (1975).
33. (a) A. I. Meyers and C. E. Whitten, *Heterocycles*, 4, 1687 (1976); (b) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, 97, 6266 (1975).
34. A. I. Meyers and G. Knaus, *Tetrahedron Lett.*, 1333 (1974).
35. (a) M. A. Hoobler, D. E. Berbreiter, and M. Newcombe, *J. Am. Chem. Soc.*, 100, 8182 (1978); (b) A. I. Meyers, E. S. Snyder, and J. J. H. Ackerman, *ibid.*, 100, 8186 (1978).
36. A. I. Meyers, A. Mazzu, and C. E. Whitten, *Heterocycles*, 6, 971 (1977).

ENZYME STEREOSPECIFICITY IN BIOSYNTHESIS

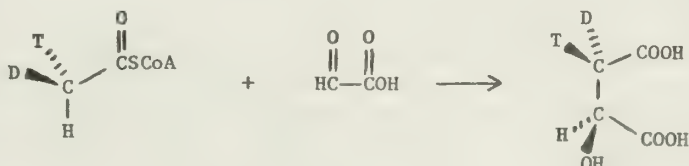
Reported by Peter Senter

April 19, 1979

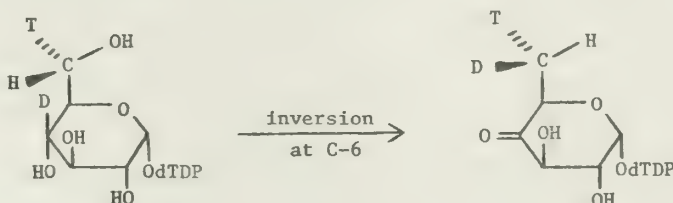
A great number of enzymatic reactions involve the reaction of achiral, torsionally symmetric functionalities such as methyl or phosphate groups. Since free rotation is possible about the bond joining a methyl or a phosphate group to the rest of the molecule, no discrimination is possible between the three terminal atoms. However, enzymatic reactions at a methyl or a phosphate group may proceed with stereospecificity, resulting in a definite spatial relationship between the group that becomes attached and the atom which it displaces.

In order to determine the stereochemistry involving methyl group transformations, it is necessary to prepare methyl groups of known configuration using all three isotopes of hydrogen. Several methods for the synthesis of chiral acetic acid have been established.^{1,2} The acetic acids thus prepared contain tracer levels of tritium, and therefore only a small fraction of the molecules are chiral.

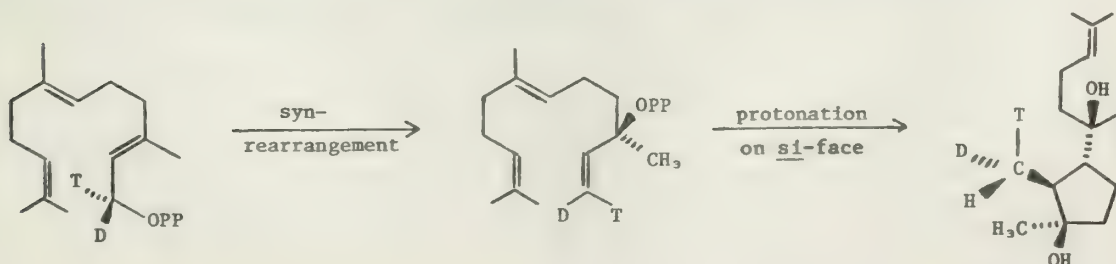
An assay which can unequivocally establish the stereochemistry of chiral acetic acid has been reported.¹ Using this procedure it is possible to deduce the stereochemistry of a reaction in which an asymmetric methyl group is produced. This assay has established that malate synthase reacts with inversion of stereochemistry at the methyl group in acetyl coenzyme A.¹



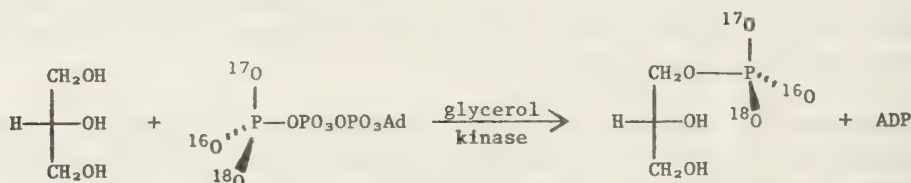
The stereochemistry of dTDP-glucose oxidoreductase proceeds with inversion of stereochemistry at the C-6 hydroxymethyl group in dTDP-glucose.³



The stereochemical ambiguities present in cyclonerodiol biosynthesis have been resolved by the determination of the chirality of a methyl group produced on protonation of labeled nerolidyl pyrophosphate.⁴



Until very recently it has not been possible to investigate the stereochemistry of enzymatic reactions on phosphorous due to the unavailability of chiral phosphate. However, methods for the preparation and stereochemical analysis of chiral phosphorothioates,⁵ and chiral phosphates having all three stable isotopes of oxygen,⁶ have been reported. A synthesis of [γ -¹⁶O,¹⁷O,¹⁸O]ATP of known configuration has recently been accomplished.^{6c} This labeled ATP has been used to demonstrate that glycerol is phosphorylated by glycerol kinase with inversion of stereochemistry at phosphorous.



In addition to all of the interesting chemistry that has evolved from research dealing with chiral methyl and phosphate groups, a great deal has been learned about the active sites of enzymes, enzyme stereospecificity, and mechanisms of enzyme mediated reactions.

BIBLIOGRAPHY

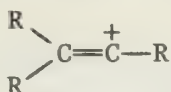
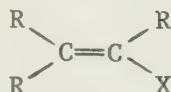
1. (a) J. W. Cornforth, J. W. Redmond, E. Eggerer, W. Buckel, and C. Gutschow, *Eur. J. Biochem.*, **14**, 1 (1970); (b) J. Luthy, J. Retey, and D. Arigoni, *Nature*, **221**, 1213 (1969).
2. (a) H. Lenz, W. Buckel, P. Wunderwald, G. Biedermann, V. Buschmeier, H. Eggerer, J. W. Cornforth, J. W. Redmond, and R. Mallaby, *Eur. J. Biochem.*, **24**, 207 (1971); (b) C. A. Townsend, T. Scholl, and D. Arigoni, *J. Chem. Soc., Chem. Commun.*, 921 (1975); (c) A. Kraus, W. Dessau, and H. Simon, *Z. Physiol. Chem.*, **357**, 1209 (1976); (d) E. Caspi and C. E. Eck, *J. Org. Chem.*, **42**, 767 (1977); (e) M. Kajiwara, S. F. Lee, A. I. Scott, M. Akhtar, C. R. Jones, and P. M. Jordan, *J. Chem. Soc., Chem. Commun.*, 967 (1978).
3. (a) C. E. Snipes, G. U. Brillinger, L. Sellers, L. Mascaro, and H. G. Floss, *J. Biol. Chem.*, **252**, 8113 (1977); (b) C. E. Snipes, C. J. Chang, and H. G. Floss, *J. Am. Chem. Soc.*, **101**, 701 (1979).
4. (a) D. E. Cane and M. S. Shiao, *J. Am. Chem. Soc.*, **100**, 3203 (1978); (b) D. E. Cane and R. Iyengar, *ibid.*, **100**, 3256 (1978); (c) D. E. Cane, R. Iyengar, and M. S. Shiao, *ibid.*, **100**, 7122 (1978); (d) D. E. Cane and R. Iyengar, *ibid.*, in press.
5. For leading references see: (a) P. M. Burgers and F. Eckstein, *Proc. Natl. Acad. Sci., U.S.A.*, **75**, 4798 (1978); (b) J. P. Richard, H. T. Ho, and P. A. Frey, *J. Am. Chem. Soc.*, **100**, 7756 (1978).
6. (a) S. R. Jones, L. A. Kindman, and J. R. Knowles, *Nature*, **275**, 564 (1978); (b) S. J. Abbott, S. R. Jones, S. A. Weinman, and J. R. Knowles, *J. Am. Chem. Soc.*, **100**, 2558 (1978); (c) W. A. Blattler and J. R. Knowles, *ibid.*, **101**, 510 (1979); (d) P. M. Cullis and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 512 (1978).

GENERATION AND UTILITY OF VINYLIC CARBOCATIONS

Reported by Michael W. Robertson

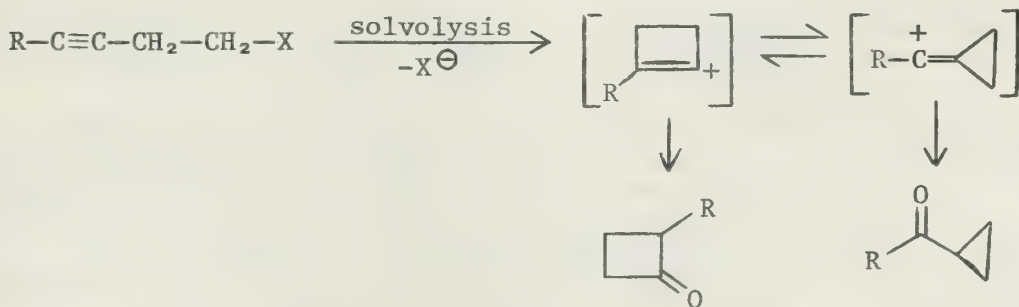
April 23, 1979

The existence of vinyl cations, 1, as discrete reactive intermediates is now well documented.^{1,2} Early mechanistic investigations on reactions such as electrophilic addition to alkynes and allenes suggested the intermediacy of these disubstituted carbenium ions.^{1a-c} A more definitive account of the chemistry of 1 has recently appeared^{2a} as a result of reports on the solvolytic generation of 1 via bond heterolysis of vinyl substrates 2. This report will summarize recent methods for the generation of 1 with applications in organic synthesis.³

12a X = OSO₂R2b X = OSO₂R_F2c X = halide

Vinyl cations have been postulated as intermediates in intermolecular electrophilic addition to arylsubstituted acetylenes.⁴⁻⁶ Depending upon the nucleophile present, synthetically useful yields of ketones⁷ and 1,1,3,3-tetrasubstituted cyclobutanes⁸ have been achieved. Several examples of intramolecular electrophilic addition to acetylenes have appeared. The "homo-propargylic rearrangement" (Scheme I) offers high yields of cyclobutanones and cyclopropyl ketones,^{2b,9} depending on the nature of the R substituent and reaction conditions. Transannular cyclization reactions of acetylenic halides¹² and biomimetic cyclization¹³ have both been proposed to occur via a vinyl cation intermediate.

Scheme I



Intermolecular electrophilic addition to allenes usually gives rise to a complex product mixture,^{1b,2b} whereas intramolecular additions ("homo-allenyl rearrangement") have shown preparative utility in the synthesis of cyclopropyl ketones¹⁰ and 2-octalones.¹¹

The generation of vinyl cations by solvolysis of vinylic substrates 2 is now widely accepted.¹⁴⁻¹⁶ This heterolytic process is possible only if two conditions are observed: (a) powerful leaving groups such as triflate or nonaflate are used or (b) there is stabilization of the resultant cation by electron releasing α -substituents. In the latter case, chloride¹⁷ and even fluoride¹⁸ have been shown to be acceptable leaving groups in vinyl cation generation. Recently, considerable attention has

been directed toward Friedel-Crafts alkylation via carbenium ions derived from 2.¹⁹ The synthetic scope of this reaction appears to be limited by the ability of 2 to undergo elimination as well as the rather harsh reaction conditions.^{19b} Intramolecular Friedel-Crafts alkylation in the synthesis of various heterocycles via the intermediacy of 1 has also been reported.²⁰

BIBLIOGRAPHY

1. (a) L. R. Subramanian and M. Hanack, *J. Chem. Ed.*, 52, 80 (1975); (b) P. J. Stang, *Prog. Phys. Org. Chem.*, 10, 205 (1973); (c) G. Modena and V. Tonellato, *Adv. Phys. Org. Chem.*, 9, 185 (1971); (d) M. Hanack, *Acc. Chem. Res.*, 9, 364 (1976); (e) Z. Rappoport, *ibid.*, 9, 265 (1976).
2. (a) P. Stang, *Acc. Chem. Res.*, 11, 107 (1978); (b) M. Hanack, *Angew. Chem. Int. Ed. Eng.*, 17, 333 (1978).
3. (a) S. A. McNeely and P. J. Kropp, *J. Am. Chem. Soc.*, 98, 4319 (1976); (b) C. A. Grob and P. Wenk, *Tetrahedron Lett.*, 4195 (1976).
4. R. C. Fahey, M. T. Payne, and D. J. Lee, *J. Org. Chem.*, 39, 1124 (1974).
5. F. Marcuzzi and G. Melloni, *J. Am. Chem. Soc.*, 98, 3295 (1975).
6. D. Kaufmann and R. Kupper, *J. Org. Chem.*, 39, 1428 (1974).
7. (a) R. W. Bott, C. Eaboin, and D. R. M. Walton, *J. Chem. Soc.*, 384 (1965); (b) D. S. Noyce, *et al.*, *J. Am. Chem. Soc.*, 87, 2295 (1965); (c) D. S. Noyce and M. D. Schiavelli, *ibid.*, 90, 1020 (1968).
8. K. Griesbaum and W. Seiter, *J. Org. Chem.*, 41, 937 (1976) and references cited therein.
9. (a) M. Hanack, J. Häffner, and I. Herterich, *Tetrahedron Lett.*, 875 (1965); (b) C. J. Collins, B. Benjamin, H. Stutz, and M. Hanack, *J. Am. Chem. Soc.*, 99, 1669 (1977); (c) M. Hanack, *et al.*, *Org. Synth.*, 54, 84 (1974); (d) H. Stutz and M. Hanack, *Tetrahedron Lett.*, 2457 (1974).
10. (a) M. Bertrand, *Bull. Soc. Chim. Fr.*, 3044 (1968); (b) M. Hanack and J. Häffner, *Tetrahedron Lett.*, 2191 (1964).
11. K. Harding, J. Cooper, and P. Puckett, *J. Am. Chem. Soc.*, 100, 993 (1978).
12. (a) M. J. Chandy, L. R. Subramanian, and M. Hanack, *Chem. Ber.*, 108, 2212 (1975); (b) Ref. 38 in ref. 2b; (c) C. E. Harding and M. Hanack, *Tetrahedron Lett.*, 1253 (1977).
13. W. S. Johnson, *Angew. Chem. Int. Ed. Eng.*, 15, 9 (1976).
14. (a) C. A. Grob and H. R. Pfaendler, *Helv. Chim. Acta*, 54, 2060 (1971); (b) L. L. Miller and D. A. Kaufman, *J. Am. Chem. Soc.*, 90, 7282 (1968); (c) Z. Rappoport and A. Gal, *ibid.*, 91, 5246 (1969); (d) P. Stang and R. Summerville, *ibid.*, 91, 4600 (1969).
15. L. J. Adzina, *U. of Illinois Seminar*, 167 (1974) and references cited therein.
16. See references 1 and 2 and references cited therein.
17. Z. Rappoport, P. Shulman and M. T. Shoolman, *J. Am. Chem. Soc.*, 100, 7041 (1978).
18. L. Eckes and M. Hanack, *Chem. Ber.*, 111, 1253 (1978).
19. (a) R. M. Roberts and M. B. Abdel-Baset, *J. Org. Chem.*, 41, 1698 (1976); (b) P. J. Stang and A. B. Anderson, *J. Am. Chem. Soc.*, 100, 1520 (1978).
20. (a) T. Sonoda *et al.*, *J. Chem. Soc. Chem. Commun.*, 612 (1976); (b) T. Sonoda *et al.*, *Bull. Chem. Soc. Jap.*, 49, 2560 (1976); (c) F. Marcuzzi and G. Molloni, *Tetrahedron Lett.*, 2771 (1975).

SEPARATION OF STERIC AND POLAR EFFECTS

Reported by Rick Gdanski

April 26, 1979

Inspired by the work of other chemists,^{1a} L. P. Hammett, in 1937,^{1b} published a treatment which successfully related chemical structures of benzene derivatives with reactivity. Physical organic chemists have since attempted to use similar relationships to relate structure with reactivity. Such treatments, including the Hammett equation, are called Linear Free Energy Relationships (LFER). Correlation of pKa's, rate constants, NMR shifts,² and other spectroscopic data³ with structure in search of LFER's have met with variable success. Taft, in 1952, published a method of quantitative separation of the effects of structure on reactivity into polar, steric, and resonance (or mesomeric) contributions.⁴ Though many data have been correlated by the substituent constants derived from this treatment,⁵ assumptions on which the treatment was based have been criticized. The subsequent development of Taft's approach by Marvin Charton is the subject of this review. Nonetheless, Taft's work was a major step forward in the elucidation of the relationships of structure with reactivity. Therefore, a brief review of his work is in order before describing alternative approaches to an analysis of the effects of structure on reactivity.

In his excellent review on the separation of polar, steric, and resonance effects, Taft⁴ uses thermodynamics and transition state theory to describe the effect of substituents on the free energies of activation of reactions. However, he points out that such a treatment does not allow one to separate the various effects of substituents. Therefore, data must be accumulated in which an observable is a function of only one effect or in which all other effects are constant. Ingold suggested,⁶ in 1930, that the basic hydrolysis of aliphatic esters $\text{RCO}_2\text{R}'$ could be used to determine the "polarity" of substituents. Taft later suggested that the acidic hydrolysis could be used as a measure of steric effects only and that the basic hydrolysis could be used in conjunction with the acidic hydrolysis as a measure of polar effects. Resonance effects could be completely ignored if one used saturated substituents since the transition state of the hydrolyses can be approximated as saturated⁷ also.

This treatment required three assumptions: (1) the relative free energies of activation may be treated as the sum of independent contributions from polar, steric, and resonance effects; (2) in the corresponding acidic and basic reactions, the steric and resonance effects are the same; and (3) the polar effects are markedly greater in the basic than in the acidic series. Thus, his steric parameter E_s is defined by Equation 1 and his polar parameter σ^* is defined by Equation 2, where k is the rate constant of a C-substituted ester, k_o is the rate constant of the $\text{MeCO}_2\text{R}'$ ester, and B and A correspond to basic and acidic hydrolysis, respectively.

$$E_s = \log \left[\frac{k}{k_o} \right]_A \quad (1)$$

$$\sigma^* \equiv \left[\frac{1}{2.48} \right] \left[\log \left[\frac{k}{k_o} \right]_B - \log \left[\frac{k}{k_o} \right]_A \right] \quad (2)$$

R' remains constant throughout a given series. The constant 2.48 is an attempt to put the σ^* constants on the same scale as the Hammett σ

constants. Taft later⁸ used the constant 5.51 in place of 2.48 to define a set of σ_I constants that would be on a proper scale with σ_p such that $\sigma_R = \sigma_p - \sigma_I$, where σ_p is for para Hammett σ 's and σ_R is the resonance contribution to σ_p .⁹ Table 1 lists a few E_s , σ^* , and σ_I values.

The first assumption is not necessarily self-evident and has received only slight criticism⁵ since this approximation is required if any progress is to be made at all. The second assumption is the heart of the treatment and is the subject of a large amount of criticism. Taft argued that the transition states for the two reaction series differ only by two protons and that their steric requirements are negligible. However, some workers feel that steric inhibition of solvation is different in the two series because of the opposite charges in the corresponding transition states.¹⁰ Most workers agree that the resonance effects are the same since the transition states are saturated and only saturated substituents are used in the treatment for E_s values. The third assumption remains valid on the grounds of the hydrolyses of p- and m- substituted benzoic esters. For the basic series, ρ is generally between +2.2 and +2.8 while for the acidic series, ρ is between -0.2 and +0.5.¹¹

The general use of Taft's E_s values and σ^* values has met with reasonable success.⁵ However, there exist many cases in which correlations are very poor or in which outlying data points cannot be easily accounted for.¹² Such cases constitute grounds for re-examination of Taft's derivation and his substituent constants. The major criticism of his work lies on the validity of his σ^* constants for alkyl groups. Much evidence has been accumulated that indicates the inductive effects of alkyl groups are constant and very near zero relative to hydrogen¹³ and that the observed effects are the result of alkyl polarizability.¹⁴ Another criticism is his procedure of defining E_s and σ^* values from the average of values determined from different reactions and in various solvents at different temperatures. This procedure has made it difficult to define new values that are on the same scale as the original values.

The most thorough re-examination of Taft's work is that of M. Charton. He first correlated E_s constants for six symmetrical substituents with the van der Waals radii r_v using Equation 3.¹⁵ The regression constant ψ is a

$$E_s = \psi r_v + h \quad (3)$$

measure of the dependence of E_s on r_v . The results of the correlation were $\psi = -2.33$, $h = 3.99$, and correlation coefficient $r = 0.996$ and indicate that E_s is indeed a steric substituent constant. Charton preferred to define a new steric parameter v from Equation 4 and calculated v values

$$v_x \equiv r_{v,x} - r_{v,H} = r_{v,x} - 1.20 \quad (4)$$

for twelve symmetrical substituents.¹⁶ He used Equation 5 to correlate the rate constants of six sets of acid-catalyzed esterification reactions

$$\log k = \psi v + h \quad (5)$$

with five v constants having values ranging from 0.00 to 1.56. The regression constant ψ is defined as a steric reaction constant. The sets contained only three or four data points each that were symmetrical, but these data give correlation coefficients ranging from 0.9990 to 0.9999.

The remaining data in the sets were used to define ν values for 42 unsymmetrical groups. Table 1 lists a few of these values. These ν values were correlated with 173 rate constants in 22 sets of esterification acid-catalyzed hydrolysis of esters, and acid-catalyzed alcoholysis of esters. The sets contained from 3 to 26 data points and had correlation coefficients ranging from 0.975 to 0.99995. The sets contained a total of 31 different substituents having ν values ranging from 0.00 for H to 1.70 for (*i*-Bu)₂CH. They included 6 different solvent systems and varied in temperature from 20 to 80°C. The success of these estimated ν values to correlate the wide range of conditions without the use of average ν values suggests that they are pure steric parameters and are an improvement over Taft's E_s values. The results also showed that the ψ 's for four of the sets used in Taft's treatment were significantly different from each other. This dictates that average E_s values defined from these sets must have significant error.

Table 1

Substituent	r_ν	E_s	ν	σ^*	σ_I
H	1.20	1.24	0.00	0.490	0.00 [†]
Me	1.715	0.00	0.52	0.000	-0.05 [†]
Et		-0.07	0.56	-0.100	-0.05 [†]
Pr		-0.36	0.68	-0.115	-0.03
<i>i</i> -Pr		-0.47	0.76	-0.190	-0.03
Bu		-0.39	0.68	-0.130	-0.04
<i>i</i> -Bu		-0.93	0.98	-0.125	-0.03
<i>s</i> -Bu		-1.13	1.02	-0.210	-0.03
<i>t</i> -Bu	2.435	-1.54	1.24	-0.300	-0.07 [†]
CF ₃	2.107	-1.16	0.91		0.42
CCl ₃	2.579	-2.06	1.38	2.65	0.43
CBr ₃	2.760	-2.43	1.56		
CI ₃	2.988		1.79		
MeO			0.36		0.25 [†]
PrO			0.56		0.27
<i>s</i> -BuO			0.86		0.26
Me ₃ Si	2.60		1.40		-0.13
F	1.47		0.27		0.52 [†]
Br	1.85		0.65		0.45 [†]

[†]Denotes Taft's original σ_I values.

Charton proceeded to show that the steric effects in base-catalyzed ester hydrolysis ψ_B are not the same as for the acid-catalyzed hydrolysis ψ_A .¹⁷ For nine sets of acid-base hydrolysis pairs containing only alkyl substituents and in which inductive effects were considered to be unimportant, he found that ψ_B was significantly larger (more negative) than ψ_A .

This result contradicts the prediction that ψ_A would be larger on the basis that the transition state for the acid-catalyzed hydrolysis contains two extra protons. It has been suggested that this discrepancy arises either from differences in solvation of the two transition states or in the positions of the two transition states. In either case, Taft's σ^* constants will be subject to some error, especially for those substituents with small values (i.e., alkyl groups). This work undermines Taft's second assumption and thereby questions the validity of the σ^* constants for alkyl groups.

Charton then found that ψ_B and ψ_A for the hydrolysis of C-substituted amides were the same¹⁸ and used these data to define sets of σ^* constants for alkyl groups at three different temperatures¹⁸ using Equation 2. The data used were obtained in the same solvent and in the same laboratory. These σ^* constants were found to have no dependence on structure and had little relationship with one another or with Taft's values. This lead Charton to the conclusion that "the Taft σ^* values for alkyl groups are artifacts."

As an alternative approach to defining inductive or polar substituent constants σ_I , Charton correlated selected pKa's of substituted acetic acids with Taft's σ_I values.¹⁹ From the regression equation defined by this correlation, Charton defined a large number of σ_I constants. Table 1 lists a few of these values. The values marked with an † are Taft's original values.⁸ This method has the advantages of being more reliable in the pKa determinations, is essentially insensitive to steric effects, requires measurement of only one number, and avoids Taft's second assumption.

Charton has also defined steric parameters for alkoxy groups ν_{ox} ,²⁰ alkyl- and dialkylamino groups $\nu_{Nx^1x^2}$,²¹ and alkylthio groups ν_{sx} .²² Many of these constants were defined in base-catalyzed reactions where the electrical effects of the alkyl groups were assumed to be constant. Since this assumption is not universally accepted,²³ its validity is in question. Nonetheless, a set of fifteen rate constants for the basic hydrolysis of ZCO_2X esters (Z and X are alkyl only) in 40% aqueous dioxane at 35°C were correlated²⁰ with Equation 6 with the following results: $\psi_1 = -2.06$, s.d. 0.0805; $\psi_2 = -2.54$, s.d. 0.0741; $h = 3.23$, s.d. 0.0822; $r = 0.995$. Independent researchers have correlated ΔG^\ddagger of rotation of N,N-dimethylamides,²⁴ base-catalyzed hydrolysis of p-

$$\log k = \psi_1 \nu_Z + \psi_2 \nu_{OX} + h \quad (6)$$

nitrophenyl esters,²⁵ and base-catalyzed hydrolysis of alkyl carboxylates²⁶ with Charton ν constants and Taft-Charton σ_I constants with excellent results. In cases where the E_s constants were also correlated,^{24,26} the ν constants were found to be as good or better than the E_s constants.

To show the utility and validity of the ν , σ_I , and σ_R constants ($\sigma_R = \sigma_p - \sigma_I$), Charton has re-examined several phenomena in which steric versus electronic effects are unclear and has obtained results which occasionally contradict longstanding ideas. In general his analysis is started by correlation of an observable Q_x with Equation 7. The coefficients α , β , and ψ are subjected to "Student t" tests for significance. The terms found to be insignificant are dropped and the data correlated

$$Q_x = \alpha \sigma_{I,x} + \beta \sigma_{R,x} + \psi \nu_x + h \quad (7)$$

with the remaining terms. Using this method, Charton has found that: (1) Taft's ortho steric substituent constants E_s^o are completely accounted for by σ_I and σ_R ,¹⁵ a result which completely contradicts the definition of E_s^o ;⁴ (2) rate constants for E2 elimination of β -alkyl-substituted 'onium compounds were found to be completely accounted for by ν ,²⁷ suggesting that the electrical effects of the alkyl groups are at least constant and that steric hindrance is the major effect of alkyl groups on the rate constants; (3) the orientation of E1 and E2 eliminations for three sets of alkyl bromides and three sets of alkyl brosylates were found to be completely accounted for by steric effects in five of the six sets;²⁷ (4) for the half-lives of racemization of 2-nitro-6-carboxy-2'-methoxybiphenyls substituted in either the 3', 4', or 5' position,²⁸ the 3' substituents exert predominantly a steric effect which has been attributed to "buttressing", the 4' substituents exert an electrical effect that is both inductive and mesomeric and shows no steric effect, and the 5' substituents exert only inductive effects.

To allow estimation of ν constants, Charton has correlated 39 ν constants for alkyl groups with the number of α , β and γ carbon atoms from the first carbon atom in the alkyl group with Equation 8.²⁹ The results are $a = 0.497$, s.d. 0.0230; $b = 0.409$, s.d. 0.0199; $c = 0.0608$, s.d. 0.0118; $i = -0.309$, s.d. 0.0457; $r = 0.986$. Since this correlation was successful,

$$\nu = a n_{\alpha} + b n_{\beta} + c n_{\gamma} + i \quad (8)$$

it suggests the possibility of correlating rate constants in a similar fashion using Equation 9. Thus, Charton has correlated the rate constants for nucleophilic substitution of benzyl chloride by alkoxide ions (set 1)

$$Q_X = a' n_{\alpha} + b' n_{\beta} + c' n_{\gamma} + i' \quad (9)$$

and of 1-chloro-2,4-dinitrobenzene by alkylamines (set 2), of alkaline hydrolysis of ethyl 4-nitrophenyl alkyl phosphonates (set 3), C-substituted amides (set 4), and dialkylphenylacetoneitriles (set 5), of the reaction of alcohols with 4-nitrobenzoylchloride (set 6), and of several other reactions with Equation 9.²⁹ The correlation coefficients are presented in Table 2. The steric coefficients obtained are analyzed in terms of percent of steric effect by Equation 10, where m refers to a' , b' , or c' . These results are also presented in Table 2.

$$P_m = \frac{m}{\sum m} \times 100 \quad (10)$$

From the data in Table 2, one notices that the effect of the α -carbons is very dependent upon the reaction type. This dependence can be thought of as a measure of steric crowding in the transition state of these reactions. Charton maintains that "the steric effect of an alkyl group is dependent on the geometry of the transition state". Therefore, as more information is gathered on the dependence of $P_{a'}$, $P_{b'}$, and $P_{c'}$ with "known" transition state structures, one might expect that Equations 9 and 10 will become useful tools in determining "unknown" transition state structures.

Table 2

Set	P _a '	P _b '	P _c '	r
1	59.5	19.7	20.8	0.956
2	92.2	7.8		0.981
3	88.4	8.9	2.7	0.974
4	44.3	55.7		0.937
5	41.9	35.8	22.3	0.962
6	74.7	20.3	5.0	0.959

Despite the success of Charton's approach to the separation of steric and polar effects, some workers feel that many of his data sets contain too few data points and therefore give deceptively high correlation coefficients.^{30,5} It is also argued that correlations should be used as tools and cannot be used in place of experiment. John Shorter has remarked concerning Charton's work,⁵ "One must not lose sight of the chemistry in a welter of statistics."

One must expect that correlation and prediction of reaction rates using Charton's approach may occasionally fail; however, this tool for probing chemical problems can also be expected to give enlightening results and is simply another step toward understanding the effects of structure on reactivity.

BIBLIOGRAPHY

1. (a) Brönsted and Pederson, *Z. Physik. Chem.*, 108, 185 (1924); (b) L. P. Hammett, *J. Am. Chem. Soc.*, 59, 96 (1937).
2. W. A. Sheppard, *Tetrahedron*, 27, 945 (1971).
3. L. S. Levitt and H. F. Widing, *Prog. Phys. Org. Chem.*, 12, 119 (1976).
4. R. W. Taft, Jr., "Steric Effects in Organic Chemistry", ed. M. S. Newman, Chapter 13, Wiley, New York, 1956.
5. N. B. Chapman and J. Shorter, "Advances in Linear Free Energy Relationships", Chapter 2, Plenum, New York, 1972.
6. C. K. Ingold, *J. Chem. Soc.*, 1032 (1930).
7. (a) M. L. Bender, *J. Am. Chem. Soc.*, 73, 1626 (1951); (b) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).
8. R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, 80, 2436 (1958).
9. D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958).
10. R. M. Noyes, *J. Am. Chem. Soc.*, 86, 971 (1964).
11. H. H. Jaffe, *Chem. Rev.*, 53, 191 (1953).
12. K. Okamoto, I. Nitta, T. Imoto, and H. Shingu, *Bull. Chem. Soc. Japan*, 40, 1905 (1967).
13. (a) C. D. Ritchie, *J. Phys. Chem.*, 65, 2091 (1961); (b) C. D. Ritchie and W. F. Sage, *Prog. Phys. Org. Chem.*, 2, 323 (1964); (c) W. Adcock and T. Khor, *J. Org. Chem.*, 43, 1272 (1978); (d) F. G. Bordwell and H. E. Fried, *Tetrahedron Lett.*, 1121 (1977).
14. (a) T. L. Brown, *J. Am. Chem. Soc.*, 81, 3229 (1959); (b) J. I. Brauman and L. K. Blair, *ibid.*, 92, 5986 (1970); (c) J. I. Brauman and L. K. Blair, *ibid.*, 91, 2126 (1969); (d) M. S. B. Munson, *ibid.*, 87, 2332 (1965).
15. M. Charton, *ibid.*, 91, 615 (1969).
16. M. Charton, *ibid.*, 97, 1552 (1975).

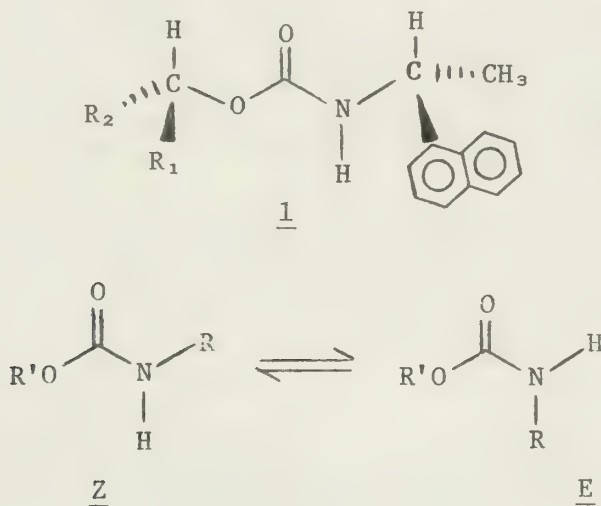
17. M. Charton, ibid., 97, 3691 (1975).
18. (a) M. Charton, J. Org. Chem., 41, 2906 (1976); (b) M. Charton, J. Am. Chem. Soc., 99, 5687 (1977); (c) M. Charton, J. Org. Chem., 44, 903 (1979).
19. M. Charton, ibid., 29, 1222 (1964).
20. M. Charton, ibid., 42, 3531 (1977).
21. M. Charton, ibid., 42, 3535 (1977).
22. M. Charton and B. Charton, J. Org. Chem., 43, 1161 (1978).
23. A. J. MacPhee and J. E. Dubois, Tetrahedron Lett., 2471 (1976).
24. M. D. Wunderlich, L. K. Leung, J. A. Sandberg, K. D. Meyer, and C. H. Yoder, J. Am. Chem. Soc., 100, 1500 (1978).
25. D. S. Kristol, R. C. Parker, and H. D. Perlmutter, J. Org. Chem., 41, 3205 (1976).
26. J. P. Idoux and J. O. Schreck, ibid., 43, 4002 (1978).
27. M. Charton, J. Am. Chem. Soc., 97, 6159 (1975).
28. M. Charton, J. Org. Chem., 42, 2528 (1977).
29. M. Charton, ibid., 43, 3995 (1978).
30. S. H. Unger and C. Hansch, Prog. Phys. Org. Chem., 12, 91 (1976).

DYNAMIC NMR STUDIES OF DIASTEREOMERIC CARBAMATES:
IMPLICATIONS TOWARD THE DETERMINATION OF RELATIVE
CONFIGURATION BY NMR AND LIQUID CHROMATOGRAPHY

Reported by Kirk Simmons

April 30, 1979

Diastereomeric carbamates similar to 1 are being used increasingly for the chromatographic resolution of racemic secondary alcohols.¹⁻⁸ Complimenting the chromatographic separability of these carbamates is the ease of retrieval of the resolved alcohol and the ability to assign the configuration of the carbinyl carbon from NMR spectral differences between the diastereomers.⁹ These spectral differences arise from the preferential population of the Z rotamer, the conformational rigidity of the carbamate backbone, and the resultant stereochemically dependent shielding by the α -naphthyl substituent.



We have previously reported that the diastereomers of type 1 carbamates have differing NMR spectral properties, depending on the configuration at the carbinyl center.⁹ On additional study we have found that some type 1 carbamates also exhibit NMR line broadening owing to a hindered rotational process about the carbonyl carbon-nitrogen bond. Since this NMR line broadening can complicate the mechanics of configurational assignments, we felt it necessary to further refine our earlier correlations of NMR spectral differences and chromatographic elution orders.⁹

Although NMR spectral differences exist between a pair of diastereomers, conformationally the diastereomers are very similar. This conformational behavior is essentially independent of the structure of the alcohol in the carbamate and is not influenced greatly by solvent polarity.

These findings are reassuring with respect to our earlier correlations of NMR spectral properties and chromatographic behavior and also demonstrate that even more information can be obtained by correlating the spectral properties of the diastereomers in the stopped exchange region.

BIBLIOGRAPHY

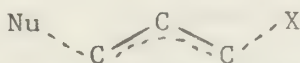
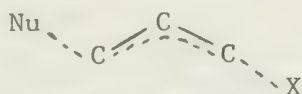
1. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, G. Keck, B. Goplan, S. Larsen, P. Siref, and J. Gras, J. Am. Chem. Soc., 100, 8034 (1978).
2. G. Schmid, T. Fukuyama, K. Alasaka, and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979).
3. T. Fukuyama, C. Wang, and Y. Kishi, J. Am. Chem. Soc., 101, 260 (1979).
4. T. Fukuyama, K. Alasaka, D. Karanewsky, C. Wang, G. Schmid, and Y. Kishi, J. Am. Chem. Soc., 101, 262 (1979).
5. W. H. Pirkle and P. E. Adams, J. Org. Chem., 43, 378 (1978).
6. W. H. Pirkle and C. W. Boeder, ibid., 43, 2091 (1978).
7. W. H. Pirkle and P. L. Rinaldi, ibid., 43, 2091 (1978).
8. W. H. Pirkle and P. L. Rinaldi, ibid., 44, 3083 (1979).
9. W. H. Pirkle and J. R. Hauske, ibid., 42, 1839 (1977).

SYN/ANTI STEREOSELECTIVITY IN S_N2' -LIKE REACTIONS

Reported by Paul Sherwin

May 3, 1979

The question of the syn/anti stereoselectivity in S_N2' -like¹ reactions has inspired a number of studies into the factors controlling the relative energies of the syn and anti transition states (Figures 1 and 2). An understanding of these factors would help not only to establish the utility of S_N2' -like reactions in stereoselective synthesis,² but also to refine theoretical models of stereoselectivity in allylic displacements.

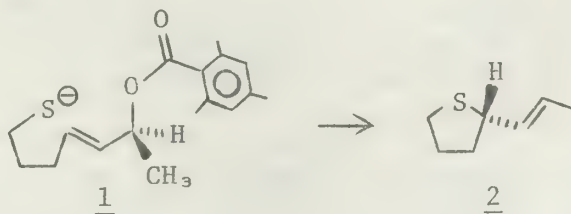
Figure 1: synFigure 2: anti

Molecular orbital studies lead to the conclusion that frontier orbital effects generally favor a syn transition state.^{3a,b} Electrostatic interactions are thought to favor syn attack with uncharged^{3b} and hydrogen-bonding nucleophiles^{3b,c} (the role of H-bonding has been questioned^{3d}), and anti attack with negatively charged nucleophiles.^{3b}

Experimental probes of S_N2' -like stereoselectivity employ stereochemical analysis of the products of S_N2' displacements on dissymmetric substrates. Studies of inter- and intramolecular S_N2' -like reactions in cyclic and acyclic systems have shown that both syn and anti products can form; the syn/anti ratio is a function of the nucleophile, the solvent, the leaving group, and counterions.

Syn attack was observed in the reactions of cyclohexenyl substrates with piperidine,^{4a-c} malonate anion,^{4a} and carboxylates;^{4d-f} of cis-dichloro-cyclobutene with methoxide ion;^{4g} of methallyl chlorides with amines;^{4h} of arene epoxides with organometallics,⁴ and in the cyclization of an allylic epoxide to form a prostaglandin precursor.^{4j}

Anti S_N2' -like attack was observed in the acetolysis of a 4-bromo-steroid^{5a} (alternative mechanisms may operate^{5b}); in the 1,6 conjugate additions of nucleophiles to arene oxides;⁴ⁱ in the cyclizations of linalyl p-nitrobenzoate to give α -terpineol,⁶ and of 1 to give 2;^{4b} in the biosynthesis of rosenonolactone;⁷ and in the reactions of cuprates with allylic and propargylic substrates.⁸



Mixtures of syn and anti products form with cyclohexenyl systems and mercaptides,^{4b} and with methallyl esters and amines.⁹ Hydride attack is syn or anti, depending on the substrate.^{8a} Chiral allenyl halides form stereoselectively syn or anti products, depending on conditions,¹⁰ although these reactions may be S_N1' examples.^{10b} Anchimeric assistance involving an intramolecular S_N2' -like attack may operate in the reactions of some

glycols,¹¹ cyclopentenyl dihalides,¹² codeine derivatives,¹³ and phenylthio cyclohexenyl esters.¹⁴

The dependence of the syn/anti product ratio on the substrate nature and reaction conditions indicates a need for a transition state model more detailed than the m.o. models. The effects of ion-pairing,¹⁵ hydrogen bonding in the transition state,^{3b-d} and conformational effects¹⁶ in S_N2' reactions have been discussed elsewhere. These approaches perhaps will provide the greatest understanding of the S_N2' stereoselectivity and pave the way to a successful predictive model.

BIBLIOGRAPHY

1. For reviews, see: F. G. Bordwell, *Acc. Chem. Res.*, 3, 281 (1970), and references cited therein.
2. See: D. Valentine and J. W. Scott, *Synthesis*, 329 (1978).
3. (a) W. Jefford and U. Burger, *Chimia*, 25, 297 (1971); (b) R. L. Yates, N. D. Epiotis, F. Bernardi, W. R. Cherry, and S. Shaik, *Top. Curr. Chem.*, 70, 126 (1977); (c) W. G. Young and I. J. Wilk, *J. Am. Chem. Soc.*, 79, 4793 (1957); (d) D. C. Dittmer and A. F. Marcantonio, *ibid.*, 86, 5621 (1964).
4. (a) G. Stork and W. N. White, *J. Am. Chem. Soc.*, 78, 4609 (1956); (b) G. Stork and A. F. Kreft, III, *ibid.*, 99, 3850, 3851 (1977); (c) A. A. Dobbie and K. H. Overton, *J. C. S. Chem. Commun.*, 722 (1977); (d) S. C. Welch, C. P. Hagan, D. H. White, W. P. Fleming, and J. W. Trotter, *J. Am. Chem. Soc.*, 99, 549 (1977); (e) L. Chiche, J. Caste, H. Cristol, and F. Plenat, *Tetrahedron Lett.*, 3251 (1978); (f) M. Ikota and B. Ganem, *J. Am. Chem. Soc.*, 100, 351 (1978); (g) W. Kirmse, F. Scheidt, and H. J. Vater, *ibid.*, 100, 3945 (1978); (h) R. M. Magid and O. S. Fruchey, *ibid.*, 99, 8368 (1977); 101, 2107 (1979); (i) A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccolo, and G. A. Berchtold, *ibid.*, 96, 6929 (1974) and references contained therein; (j) J. Martel, A. Blade-Font, C. Marie, M. Vivat, E. Toromanoff, and J. Buendia, *Bull. Soc. Chim. Fr.*, 131 (1978).
5. (a) J. Y. Satoh and T. T. Takahashi, *Chem. Commun.*, 1714 (1970); (b) R. B. Warneboldt and L. Weiler, *Tetrahedron Lett.*, 3413 (1971).
6. S. Godtfredsen, J. P. Obrecht, and D. Arigoni, *Chimia*, 31, 62 (1977).
7. D. E. Cane and P. P. N. Murthy, *J. Am. Chem. Soc.*, 99, 8329 (1977).
8. (a) See footnote 19 in reference 4h (1979); (b) P. Vermeer, H. Westmijze, H. Kleijn, and L. A. Van Dijck, *Recl. Trav. Chim. Pays-Bas*, 97, 56 (1978).
9. T. Oritani and K. H. Overton, *J. C. S. Chem. Commun.*, 454 (1978).
10. (a) O. J. Muscio, Y. M. Jun, and J. B. Philip, Jr., *Tetrahedron Lett.*, 2379 (1978); (b) S. R. Landor, B. Demetrious, R. J. Evans, R. Grzeskowiak, and P. Davey, *J. C. S. Perkin II*, 1995 (1972).
11. J. Cleophax, D. K. Duc, J. M. Dalaumeny, S. D. Gero, and A. Rolland, *J. C. S. Chem. Commun.*, 771 (1978).
12. A. C. Cope, L. L. Estes, J. R. Emery, and A. C. Haven, *J. Am. Chem. Soc.*, 73, 1199 (1951).
13. K. Abe, M. Onda, and S. Okuda, *J. C. S. Perkin I*, 316 (1973).
14. J. J. Uebel, R. F. Milaszewski, and R. E. Arlt, *J. Org. Chem.*, 42, 585 (1977).
15. (a) R. A. Sneen, *Acc. Chem. Res.*, 6, 46 (1973); (b) C. Georgoulis and G. Ville, *J. Chem. Res. (M)*, 3341 (1978).
16. E. Toromanoff, *Tetrahedron*, 34, 1665 (1978).

ANION-ASSISTED OXY-COPE REARRANGEMENTS

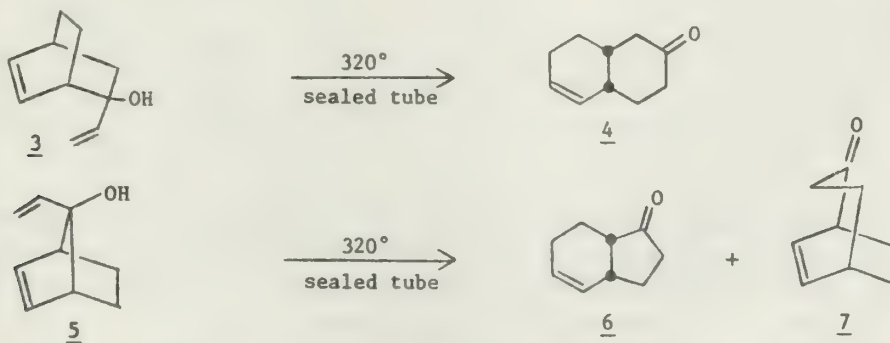
Reported by Clark Cummins

May 10, 1979

The use of pericyclic reactions has become one of the main synthetic tools available to the organic chemist, especially since the advent of a fundamental understanding of these processes in terms of orbital symmetry.¹ Next to the Diels-Alder reaction, probably the most useful of these types of reactions are the [3,3] sigmatropic rearrangements. The ability to effect complex molecular reorganization with a high degree of regio- and stereochemical control makes this type of process applicable to many organic studies. The prototype for these rearrangements is the Cope rearrangement of 1,5 hexadienes $\underline{1} \rightarrow \underline{2}$ (X=H).^{2,3} This is thought to be a concerted process, though evidence exists for radicals or radicaloid species in certain cases.³ Substitution of a heteroatom for carbon at the 3-position of $\underline{1}$, and rearrangement of these systems has been widely investigated (Claisen,⁴ aza-Claisen,⁵ thia-Claisen⁶). Systems with more than one heteroatom have also been studied.⁷ Another interesting variation of the Cope process is the oxy-Cope rearrangement $\underline{1} \rightarrow \underline{2}$ (X=OH). The end product, after tautomerization, is a δ,ϵ unsaturated aldehyde.

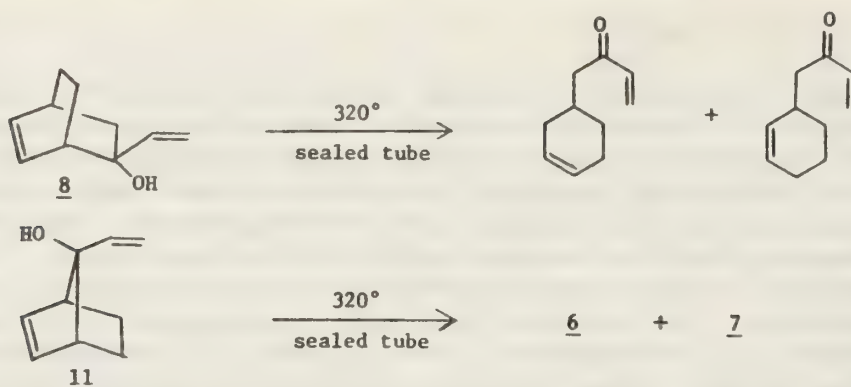


The term "oxy-Cope rearrangement" was first applied to the reaction observed in 1964 by Berson and Jones in the thermolysis of 2-endo-vinyl-2-exo-hydroxy-bicyclo[2.2.2]oct-5-enes ($\underline{3}$) and syn-7-vinyl-anti-7-hydroxy norbornenes ($\underline{5}$).⁸ Pyrolysis of $\underline{3}$ gave as the major product the oxy-Cope rearranged compound $\underline{4}$, while pyrolysis of $\underline{5}$ gave the oxy-Cope rearrangement product $\underline{6}$, and the product of [1,3] sigmatropic rearrangement $\underline{7}$, in a ratio of 1:14, respectively.

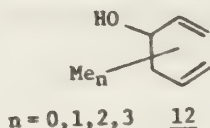


Pyrolysis of 2-exo-vinyl-2-endo-hydroxybicyclo[2.2.2]oct-5-ene ($\underline{8}$) led to $\underline{9}$ and $\underline{10}$ as the major products. Incomplete pyrolysis of mixtures of $\underline{3}$ and $\underline{8}$ at three different temperatures led to recovery of starting material with no change in relative composition, indicating that the rates of rearrangement of $\underline{3}$ and $\underline{8}$ are virtually identical. Pyrolysis of anti-7-vinyl-syn-7-hydroxynorbornene ($\underline{11}$) led to $\underline{6}$ and $\underline{7}$ (and other by-products) in a ratio of 1:19. Incomplete pyrolysis of mixtures of $\underline{5}$ and $\underline{11}$ at different temperatures again gave no change in relative composition of starting material, indicating identical rearrangement rates. These

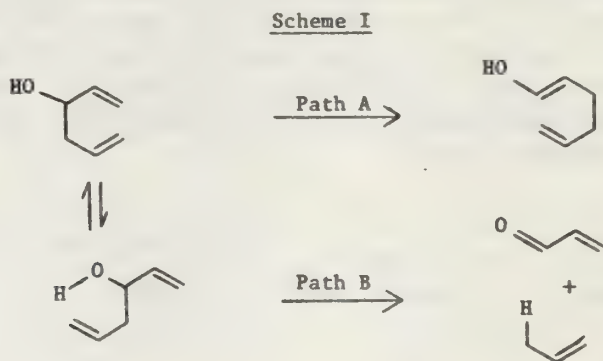
observations are incompatible with concerted rearrangement, but consistent with a diradical mechanism.



In 1967, Viola and co-workers studied the pyrolysis of mono-, di-, and tri- methyl substituted 3-hydroxy-1,5-hexadienes 12.⁹ In all cases



the products obtained could be explained by two different concerted rearrangement pathways, as illustrated for the parent unsubstituted compound in Scheme I. Path A shows the oxy-Cope rearrangement, while Path B shows the well-documented β -hydroxy olefin cleavage.¹⁰ Pyrolysis

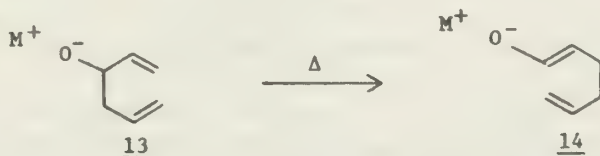


of the unsubstituted hydroxy diene 12 ($n=0$) gave 60% rearrangement and 40% cleavage. Examination of the steric effects of methyl substitution in system 12 on the conformational equilibrium of the chair-like transition states preferred for pericyclic rearrangement¹¹ leads to a qualitative understanding of the relative ratios of oxy-Cope rearrangement and β -hydroxy olefin cleavage products in the various substituted cases. Radicals are mechanistically ruled out by the absence of cross-coupled products expected at the high temperatures used (320° - 390°).

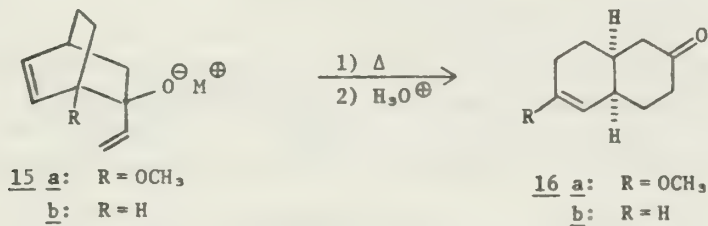
These seemingly inconsistent results can be reconciled if one examines the bicyclic compounds 3, 5, 8, and 11 more closely. Only 3 and 5 have the possibility of forming the cyclic transition state necessary for concerted rearrangement. In both cases they can only attain a boat-like conformation. Even though rearrangement through a boat-like transition state would normally be energetically more favorable than bond scission to a diradical

species,^{11,12} it has been shown¹³ that an α -oxy substituent lowers the activation energy for bond homolysis. In this case the energy decrease is apparently sufficient for the biradical mechanism to become the most favorable energetically. In general, though, unless complicating steric factors intervene (as in the above bicyclic case), the oxy-Cope is likely to proceed by a concerted process.

In 1975 Evans and Golob reported a study of the oxy-Cope rearrangement of 1,5 hexadiene alkoxides 13 \rightarrow 14.¹⁴ The models they chose for



this study were the [2.2.2] bicyclooctenes 15a and 15b, as kinetic data on the oxy-Cope rearrangement of the parent dienols was available.^{8a,15} Although the lithium and magnesium bromide alkoxides ($M = \text{Li}, \text{MgBr}$) showed



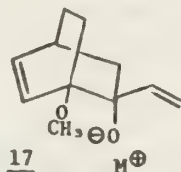
no signs of rearrangement after being heated at reflux in THF (66°) for 24 hours, the sodium alkoxide 15a ($M = \text{Na}$) rearranged to methoxy ketone 16a with a half life of 1.2 hr. The potassium alkoxide 15a ($M = \text{K}$) showed an incredible rate enhancement over dienol rearrangement, and gave methoxy ketone 16a in $\geq 98\%$ yield with a calculated half life of 1.4 min. This rate dependence on counterions suggested that further acceleration could be affected by the used of crown ethers. The rearrangement of 15a ($M = \text{K}$) in THF at 0° showed a limiting rate enhancement of 180 as varying amounts of 18-crown-6 were added, the value of 180 being reached with the addition of 3 equivalents. This same value of 180 was obtained in a study of the rearrangement of 15a ($M = \text{K}$) in HMPA. These data indicate that a maximal rate acceleration is obtained by ion-pair dissociation, and also indicate that rate dependence on solvent dielectric is minimal. First order rate constants determined at four temperatures gave the information listed in Table 1. This allows comparison of rate data between the alkoxide and parent alcohol. At 25° , the rearrangement of 15a ($M = \text{H}$) vs. 15a ($M = \text{K}$)

Table 1

Substrate	E_a , kcal/mole	Log A, kcal/mole	Temp. Range, $^\circ\text{K}$
<u>13a</u> $M = \text{H}$	35.9 ± 1.8	12.6 ± 0.6	448-488
<u>13a</u> $M = \text{K}$	19.4 ± 0.7	10.3 ± 0.4	282-328
<u>13a</u> $M = \text{K}^*$	18.2 ± 0.1	11.5 ± 0.1	253-278
<u>13b</u> $M = \text{H}$	41.8 ± 0.4	12.5 ± 0.2	—

* 1.1 equivalents of 18-crown-6 added

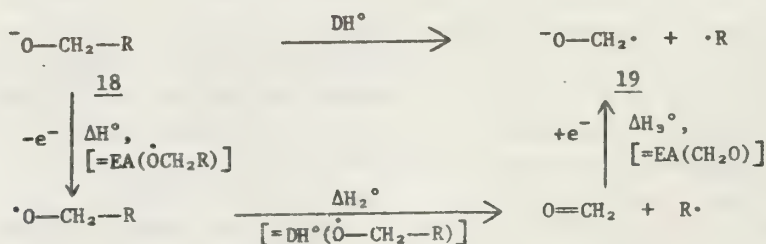
with the addition of 1.1 equivalents of 18-crown-6 shows a rate acceleration of 10^{12} . The rearrangement of 15b ($M=H$) vs. 15b ($M=K$) at 40° shows a rate acceleration of 10^{12} , and at 0° in the presence of crown ether an acceleration of 10^{17} . It is interesting to note that diene alkoxide 17 ($M=K$) shows no rearrangement after heating for 24 hr. This observation implies a concerted mechanism, though not excluding radical intermediates.



While there have been other reports in the literature of facile Cope rearrangements,¹⁶ and even alkoxide assisted Cope rearrangements,¹⁷ they were isolated examples, and did not receive much attention. This quantitative study by Evans, however, with its remarkable rate data, has stimulated a great deal of interest in this reaction. Specifically, the questions of the origin of the rate enhancement, the mechanism of the process, and its potential synthetic utility are raised.

In an effort to understand the nature of the alkoxide effect on the oxy-Cope rearrangement, Evans and Baillargeon studied the gas phase dissociation energy of the conversion 18 to 19.¹⁸ A simple Born-Haber cycle was established, as shown in Scheme II, and using experimentally determined

Scheme II



bond dissociation energies and electron affinities, the bond dissociation energies (DH°) of some alkoxides were calculated. The results are shown in Table 2. The data shows an impressive ΔD , the dissociation energy

Table 2

Substrate	$\text{DH}^\circ(\text{HO}-\text{CH}_2-\text{R})$, kcal/mole	$\text{DH}^\circ(\text{O}-\text{CH}_2-\text{R})$, kcal/mole	ΔD , kcal/mole
<u>18</u> , $\text{R} = \text{H}$	93	76	17
<u>18</u> $\text{R} = \text{CH}_3$	83	68	15
<u>18</u> $\text{R} = \text{CH}_2-\text{CH}=\text{CH}_2$	71	58	13

difference between the alcohol and alkoxide, of 13-17 kcal/mole. This is attributed to differential stabilization of the radical by overlap with the orbitals of the oxygen species. Calculations indicate that this overlap is more effective for the radical alkoxide than for the radical alcohol.¹⁹ The effects of various counterions are unknown, though predictions are that the charge-localized alkoxide will experience greater stabilization than the charge-delocalized ketyl. Thus, one might predict that if the oxy-Cope rearrangement proceeds through a transition state resembling a ketyl-like species, then decreasing the electronegativity

of the metal counterion (K instead of Na or Li) and increasing the cation solvating ability of the medium (crown ethers) should decrease the net stabilization of the ground state relative to the transition state due to the counterions, and increase the rate. The predictions are born out in the experimental results, but this does not necessarily prove the preceeding ex-post facto argument, since no quantitative estimates of counterion effects on alkoxide homolysis are available.

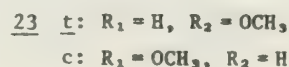
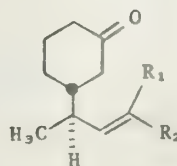
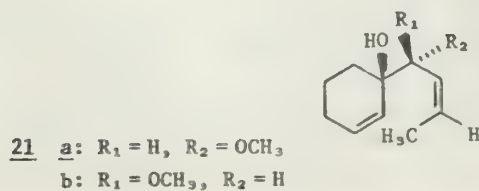
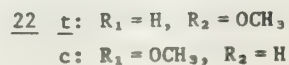
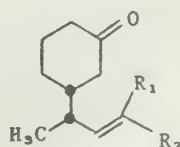
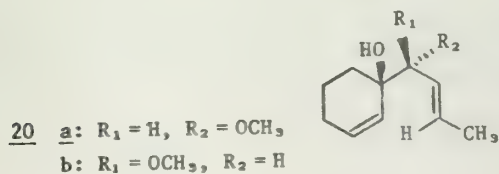
Ab-initio theoretical calculations of alcohol and alkoxide homolysis agree with the thermochemical results, and these are shown in Table 3. The comparison of the theoretical bond association energy difference relative to methanol of the alkoxide, with a value of 16.5 kcal/mole, to the corresponding thermochemical value, 17 kcal/mole, shows the close correlation. These calculations indicate a counterion effect qualitative in agreement with the earlier prediction, but in this case based on weakening the C-H bond by increasing delocalization of charge from the oxygen to the carbon.

Table 3

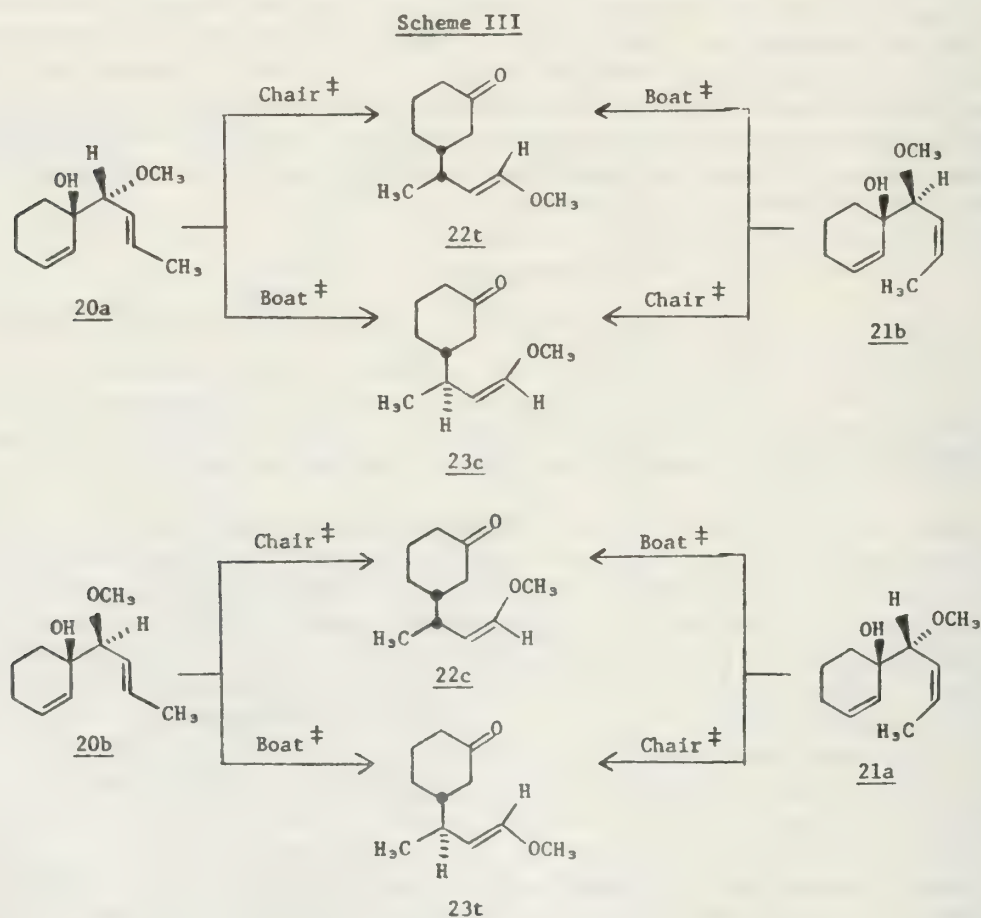
Substrate	Bond Energy, kcal/mole	ΔD (Relative to MeOH), kcal/mole
H ₃ CONa	80.6	10.1
H ₃ COK	79.0	11.7
H ₃ CO [⊖]	74.2	16.5

Thus, it is clear that the alkoxide has a weakening effect on the adjacent carbon-carbon bond, and can accelerate bond homolysis by destabilization of the ground state. However, the thermochemical and theoretical calculations yield an energy value which cannot account for the observed rate enhancement.²⁰ It thus appears unlikely that a radical mechanism is involved. This is supported by other work of Evans and Baillargeon in which thermochemical estimates of activation energies have ruled out a radical or ionic mechanism.²⁰ Apparently, the rate enhancement is due not only to ground state destabilization, but also to transition state stabilization, perhaps due to developing formation of the product enolate.

While the effect of the alkoxide on the rate of the oxy-Cope process was now better understood, the mechanism of the accelerated reaction was not. In order to determine whether or not the reaction was concerted, Evans and Nelson undertook a stereochemical study.²¹ They chose to study the anion-accelerated oxy-Cope rearrangements of the two pairs of diastereomeric dienols, 20a, 20b and 21a, 21b, to the ketones 22t, 22c and 23t, 23c.



Although at the onset of the work complete stereochemical assignments had not been made on the pairs of dienols, the reasoning was made that if all of the dienols underwent concerted rearrangement only, then from each dienol only two possible products could result. One would be formed via the chair transition state and one via the boat transition state, the amounts indicating the relative energies of the two transition states. This pattern is illustrated in Scheme III. If any one dienol gave more than 2 ketone products, or a product not derivable by either a chair or boat transition state, this would be definitive proof of a non-concerted rearrangement pathway.



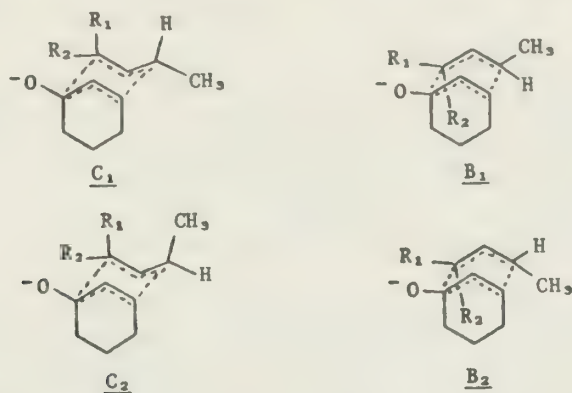
The dienols were rearranged using potassium hydride in diglyme at 110° for 38 hr. Products were separated by column chromatography and gas chromatography. The results of this study are shown in Table 4. The

Table 4

Dienol	Product Composition, %			
	22t	23c	22c	23t
<u>20a</u>	96	4	<1	<1
<u>20b</u>	<1	<1	77	28
<u>21a</u>	<1	0-2	2-0	98
<u>21b</u>	30	70	<1	<1

data very strongly suggest a concerted pathway for the rearrangement, showing essentially complete transfer of chirality and olefin geometric control. The difference in the ratio of cis:trans olefin geometry in the

rearrangement of 20a to 20b, as well as 21a to 21b, can be understood by examining the transition states. Structures C₁ and B₁ are the chair and boat transition states, respectively, for compounds 20a and 20b. In both cases, the chair transition state is conformationally more stable. For



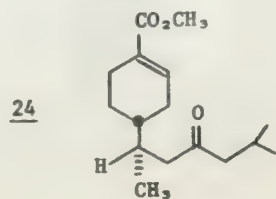
20a, $R_1 = H$, whereas for 20b, $R_1 = OCH_3$, and thus C₁ for 20b is less stable than C₁ for 20a, due to the pseudo-axial methoxy substituent, and $\Delta\Delta G^\ddagger$, the free energy difference between the chair and boat transition states, is smaller for 20b than 20a. Therefore, 20b shows less preference for the chair transition state than does 20a, and the cis-trans product ratios for the rearrangements of 20a and 20b reflect this. Structures C₂ and B₂ are the chair and boat transition states, respectively, for 21a and 21b. The same analysis predicts a larger preference for the chair transition state by 21a than 21b and also consistent geometric ratios.

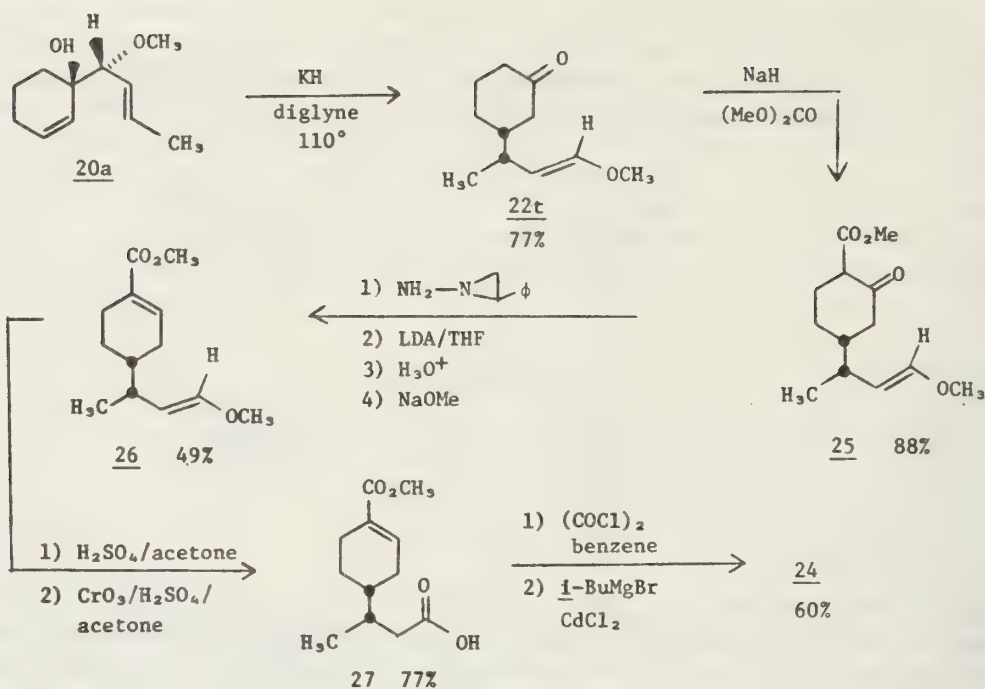
This study shows that the anion-assisted oxy-Cope rearrangement has all of the stereochemical requirements of a pericyclic reaction, and this strongly suggests that the mechanism is a concerted one. It therefore seems that, although the rate of the oxy-Cope rearrangement is enhanced by a factor of 10^{12} - 10^{17} by use of the alkoxide, the mechanism remains unchanged.

The [1,3] sigmatropic rearrangement of potassium alkoxides has also been reported,²² and rate enhancements of 10^{15} - 10^{17} are observed. Whether this also is a concerted process remains in question, however, as a comprehensive mechanistic study of these rearrangements has not been published.

As with all pericyclic processes, the capacity for the oxy-Cope rearrangement to afford products of controlled stereochemistry has made it a very attractive tool for the synthetic chemist. The utility of this reaction has been hampered by the high temperatures necessary, and the accompanying side reactions, such as β -hydroxy olefin cleavage. The advent of the alkoxide promoted rearrangement has allowed the use of this process in solution at room temperature and, except in the case of highly sterically congested systems, leads to much better rearrangement yields.⁹ This has resulted in its use in a number of natural product syntheses.

Evans and Nelson have reported a synthesis of (\pm)-erythro-juvabione (24),²¹ which depends on an anion-assisted oxy-Cope rearrangement to establish its stereochemistry. The synthetic pathway is outlined in the conversion of 20a to 24.





The key step is the rearrangement of 20a to 22t, establishing both contiguous stereochemical centers. Carbomethoxylation, Bamford-Stevens reduction and isomerization affords the α,β -unsaturated ester 26. Hydrolysis of the enol ether, oxidation to the carboxylic acid, conversion to the acid chloride, and reaction with diisobutyl cadmium yields (\pm)-erythro-juvabione 24 in a stereochemically controlled fashion.

The accelerated oxy-Cope process has also found use in the synthesis of germacranol sesquiterpenes,²³ steroids,²⁵ perhydrozulenenes,²⁶ preparation of 1,6 dicarbonyl compounds,²⁷ quinone isoprenylation reactions,²⁸ and other endeavors.²⁹ In addition to providing potential synthetic routes to previously hard-to-obtain molecules, it has also yielded valuable mechanistic information which may be a key in understanding other complex molecular rearrangements.

BIBLIOGRAPHY

1. (a) R. B. Woodward and R. Hoffman, *J. Am. Chem. Soc.*, **87**, 395 (1965); (b) R. B. Woodward and R. Hoffman, *ibid.*, **87**, 2511 (1965).
2. S. J. Rhoads and N. R. Raulins, "Organic Reactions", Vol. 22, John Wiley and Sons, Inc., New York, 1975, pp. 1-252.
3. R. Wehrli, D. Bellus, H. Hansen, and H. Schmid, *Chimia*, **30**, 416 (1976).
4. L. Claisen, *Ber. Dtsch. Chem. Ges.*, **45**, 3157 (1912).
5. B. S. Thayagarajan, "Advances in Heterocycles", A. Katritzky, ed., Academic Press, New York, 1967, Vol. 8, p. 143.
6. (a) H. Kwart and T. J. George, *J. Chem. Soc. Chem. Commun.*, 433 (1970); (b) K. Kondo and O. Ojima, *ibid.*, 62 (1972).
7. R. M. Coates and I. M. Said, *J. Am. Chem. Soc.*, **99**, 2355 (1977).
8. (a) J. Berson and M. Jones, *ibid.*, **86**, 5017 (1964); (b) J. Berson and M. Jones, *ibid.*, **86**, 5019 (1964).
9. A. Viola, E. James Iorio, Katherine K. Chen, George M. Glover, Ulhas Nayak, and Phillip J. Kacinski, *ibid.*, **89**, 3462 (1967).

10. (a) R. T. Arnold and G. Smolinsky, *ibid.*, 81, 6443 (1959); (b) R. T. Arnold and G. Smolinsky, *J. Org. Chem.*, 25, 129 (1960); (c) G. G. Smith and R. Taylor, *Chem. Ind. (London)*, 949 (1961); (d) G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965).
11. W. v. E. Doering and W. R. Roth, *Tetrahedron*, 18, 67 (1962).
12. (a) R. B. Woodward and T. J. Katz, *Tetrahedron*, 5, 70 (1954); (b) R. C. Cookson, N. S. Isaacs, and M. Szelke, *ibid.*, 20, 717 (1964); (c) G. S. Hammond and R. D. Boer, *J. Am. Chem. Soc.*, 86, 899 (1964); (d) D. J. Trecker and J. P. Henry, *ibid.*, 86, 902 (1964).
13. (a) E. G. Foster, A. C. Cope, and F. Daniels, *J. Am. Chem. Soc.*, 69, 1893 (1947); (b) G. R. Aldridge and G. W. Murphy, *ibid.*, 77, 11 (1951).
14. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 97, 4765 (1975).
15. D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 137 (1972).
16. (a) P. Yates and P. Eaton, *Tetrahedron Lett.*, 11, 5 (1960); (b) R. C. Cookson, J. Hudec, and R. O. Williams, *ibid.*, 22, 29 (1960); (c) R. Breslow and J. M. Hoffman, Jr., *J. Am. Chem. Soc.*, 94, 2111 (1972).
17. (a) S. Swaminathan, J. P. John, and S. Ramachandran, *Tetrahedron Lett.*, 729 (1962); (b) S. Swaminathan, K. G. Srinivasan, and P. S. Venkataramani, *Tetrahedron*, 26, 1458 (1970).
18. (a) D. A. Evans and D. J. Baillargeon, *Tetrahedron Lett.*, 3315 (1978); (b) D. A. Evans and D. J. Baillargeon, *ibid.*, 3319 (1978).
19. M. L. Steigerwald, W. A. Goddard, III, and D. A. Evans, *J. Am. Chem. Soc.*, 101, 1994 (1979).
20. D. J. Baillargeon, Ph.D. Thesis, California Institute of Technology, 1974.
21. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.*, in press.
22. (a) R. W. Thies and E. P. Seitz, *J. Chem. Soc. Chem. Commun.*, 846 (1976); (b) S. R. Wilson, D. T. Mao, K. M. Jernberg, and S. T. Ezmiry, *Tetrahedron Lett.*, 2559 (1977); (c) S. R. Wilson and D. T. Mao, *J. Chem. Soc. Chem. Commun.*, 479 (1978); (d) R. W. Thies and E. P. Seitz, *J. Org. Chem.*, 43, 1050 (1978).
23. W. C. Still, *J. Am. Chem. Soc.*, 99, 4186 (1977).
24. W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, 34, 3587 (1969).
25. M. E. Jung and J. P. Hudspeth, *J. Am. Chem. Soc.*, 100, 4309 (1978).
26. H. O. House, T. S. B. Sayer, and C. Yau, *J. Org. Chem.*, 43, 2153 (1978).
27. (a) D. Seebach, K. Geiss, and M. Pohrakotr, *Angew. Chem. Int. Ed. Eng.*, 15, 437 (1976); (b) D. A. Evans, D. J. Baillargeon, and J. V. Nelson, *J. Am. Chem. Soc.*, 100, 2242 (1978).
28. D. A. Evans and J. M. Hoffman, *J. Am. Chem. Soc.*, 98, 1983 (1976).
29. (a) L. S. Hegedus and B. R. Evans, *J. Am. Chem. Soc.*, 100, 3461 (1978); (b) T. Miyashi, A. Hazato, and T. Mukai, *ibid.*, 100, 1008 (1978); (c) G. A. Kraus and K. Frazier, *Synthetic Comm.*, 8, 483 (1978); (d) D. Gange and P. Magnus, *J. Am. Chem. Soc.*, 100, 7746 (1978).

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